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FILE LAST UPDATED: 7 May 2010 (20100507/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2010

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the first quarter of 2010.

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=> s bioisostere?

L1 690 BIOISOSTERE?

=> s l1 and methyl and hydrogen

1144383 METHYL

767 METHYLS

1144838 METHYL

(METHYL OR METHYLS)

1032231 ME

12150 MES

1040139 ME

(ME OR MES)

1805973 METHYL

(METHYL OR ME)

1203618 HYDROGEN

6623 HYDROGENS

1207264 HYDROGEN

(HYDROGEN OR HYDROGENS)

L2 21 L1 AND METHYL AND HYDROGEN

=> s l2 and review/dt

2374978 REVIEW/DT

L3 0 L2 AND REVIEW/DT

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L2 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:980954 HCAPLUS

TITLE: 1,5-C-Thio-sugars as selective inhibitors of
thioredoxins

AUTHOR(S): Witczak, Zbigniew J.

CORPORATE SOURCE: Dept. of Pharmaceutical Sciences, Wilkes University,
Wilkes-Barre, PA, 18766, USA

SOURCE: Abstracts of Papers, 238th ACS National Meeting,
Washington, DC, United States, August 16-20, 2009
(2009), CARB-128. American Chemical Society:
Washington, D. C.

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CODEN: 69LVCL

DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)

AB The biol. activities of thioredoxin reductase TRX and thioredoxins TX and their apparent relevance to aggressive tumor growth suggest that this system may be an attractive target for cancer therapy. Of currently available chemotherapeutics agents, cis platin may directly affect the TRX/TX system. Carmustine (BCNU) and other nitrosourea drugs and disulfides such as PX-12 are well known inhibitors of TRX/TX system. In our laboratory we have developed a new coupling reaction of functionalized new class of reactive thiols derived from highly reactive enone 3 with reactive carbohydrate thiols 4a-c in the presence of a catalytic amount of piperidine or tetra-Me guanidine (TMG) in polar solvent systems MeCN, THF. The regiochem. of the Michael addition stereoselectively produced 1, 4 adducts 5a-c. These adducts 5a-c, upon the conventional oxidation under mild conditions (diluted hydrogen peroxide in acetone), afford disulfides 6a-c as new candidates for inhibition study of TRX/TX system. This presentation will summarize recent developments in the biol. and chemical functionalization of bioisosteres of new carbohydrate disulfide analogs, from three major carbohydrate families (L-arabinose, D-galactose and D-lactosamine). Progress toward the design and discovery of TRX/TX system specific inhibitors will be discussed as well.

L2 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:31564 HCAPLUS

DOCUMENT NUMBER: 142:316682

TITLE: Dopamine D1/D5 Receptor Antagonists with Improved Pharmacokinetics: Design, Synthesis, and Biological Evaluation of Phenol Bioisosteric Analogues of Benzazepine D1/D5 Antagonists

AUTHOR(S): Wu, Wen-Lian; Burnett, Duane A.; Spring, Richard; Greenlee, William J.; Smith, Michelle; Favreau, Leonard; Fawzi, Ahmad; Zhang, Hongtao; Lachowicz, Jean E.

CORPORATE SOURCE: Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA

SOURCE: Journal of Medicinal Chemistry (2005), 48(3), 680-693
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

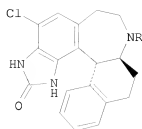
DOCUMENT TYPE: Journal

LANGUAGE: English

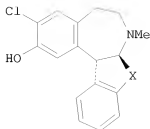
OTHER SOURCE(S): CASREACT 142:316682

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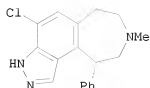
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I



II



III

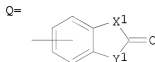
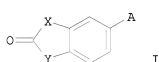
AB Nonracemic fused benzazepines and naphthazepines such as I (R = H, Me) are prepared as selective dopamine D1 and D5 receptor antagonists with improved bioavailability over related high affinity dopamine D1 and D5 receptor antagonists by replacement of the phenol moiety in II (X = CH₂CH₂) with a variety of fused hydrogen-bond donating moieties. Benzazepines in which the hydrogen bond donor is pointed approx. parallel to an axis through the benzazepine nitrogen and the benzo ring are more effective as selective dopamine D1 and D5 receptor antagonists than benzazepines in which the hydrogen bond donor is pointed away from the axis. Attempts to replace the phenol group in a benzazepine II (X = H₂) with a bioisostere lead to decreased binding to the desired dopamine receptors; an indazolobenzazepine III is an active dopamine D1 and D5 receptor antagonist. I (R = H, Me) show improved pharmacokinetic behavior over II (X = CH₂CH₂) in rats; III shows similar pharmacokinetic behavior in rats to II (X = H₂).

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REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN
 ACCESSION NUMBER: 2003:633679 HCAPLUS
 DOCUMENT NUMBER: 139:180055
 TITLE: Preparation of benzoxazoline derivatives as catechol bioisosteres
 INVENTOR(S): Gazit, Aviv; Levitzki, Alexander; Blum, Galia
 PATENT ASSIGNEE(S): Yissum Research Development Company of the Hebrew University of Jerusalem, Israel
 SOURCE: PCT Int. Appl., 74 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|--|-----------------|------------|
| WO 2003066608 | A1 | 20030814 | WO 2003-IL94 | 20030205 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
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| AU 2003206109 | A1 | 20030902 | AU 2003-206109 | 20030205 |
| EP 1472237 | A1 | 20041103 | EP 2003-702993 | 20030205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| JP 2005526026 | T | 20050902 | JP 2003-565982 | 20030205 |
| US 20050143430 | A1 | 20050630 | US 2004-914010 | 20040805 |
| PRIORITY APPLN. INFO.: | | | US 2002-354153P | P 20020206 |
| | | | WO 2003-IL94 | W 20030205 |
| OTHER SOURCE(S): | | CASREACT 139:180055; MARPAT 139:180055 | | |
| GI | | | | |



AB The present invention provides catechol bioisostere compds. (I) [X and Y are independently NR1 or O, wherein R1 is H or alkyl; A is a group represented by the formula -COC(CN):CH-B, CH:C(CN)Me; wherein B is Ph which is unsubstituted or substituted by one or more OR2 or CO2R3 (wherein R2 and R3 are independently hydrogen or alkyl), or B is a group represented by the formula Q (wherein X1 and Y1 are independently NR1 or O, wherein R1 is H or alkyl); D is cyano or C(O)R4 (wherein R4 is an alkyl, aralkyl or aryl which is unsubstituted or substituted by one or more OR5, wherein R5 is hydrogen or alkyl; or C(O)NR6R7; wherein R6 and R7 are independently hydrogen or an optionally substituted alkyl, aralkyl or aryl)] which are potent inhibitors of protein tyrosine kinases (PTKs). The present invention further provides methods of inhibiting PTKs, for example receptor protein tyrosine kinases (RTKs), comprising administering the catechol bioisosteres. The catechol bioisostere compds. I are useful in treating or preventing PTK-related disease states, particularly protein tyrosine kinase related disorders which are associated with defects in signaling pathways mediated by PTKs. Thus, 20 mg 3-(2-oxobenzoxazolin-6-yl)-3-oxopropanenitrile, 13.6 mg 3,4-dihydroxybenzaldehyde, and 1.22 mg β -alanine in 10 mL ethanol were refluxed for 4.5 h, evaporated, and purified by HPLC using a semipreparative RP18 column to give 3-(3,4-dihydroxyphenyl)-2-(2-oxobenzoxazolin-6-

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ylcarbonyl)acrylonitrile (II) and its isomer in 38 and 5%, resp. II and 2-(3,4-dihydroxybenzoyl)-3-(2-oxobenzoxazolin-5-yl)acrylonitrile vitro showed IC50 of 1.2 µM and 70 nM for inhibiting an insulin-like growth factor 1 receptor (IGF-IR).

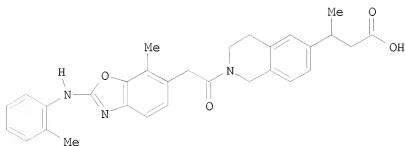
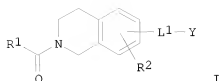
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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:946114 HCAPLUS
DOCUMENT NUMBER: 138:24648
TITLE: Substituted tetrahydroisoquinolines for use in the treatment of inflammatory diseases
INVENTOR(S): Fenton, Garry; Harris, Neil Victor
PATENT ASSIGNEE(S): Aventis Pharma limited, UK
SOURCE: PCT Int. Appl., '77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------------------|----------|-----------------|------------|
| WO 2002098426 | A1 | 20021212 | WO 2002-GB2517 | 20020605 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2449402 | A1 | 20021212 | CA 2002-2449402 | 20020605 |
| CA 2449402 | C | 20090811 | | |
| AU 2002302783 | A1 | 20021216 | AU 2002-302783 | 20020605 |
| AU 2002302783 | B2 | 20061116 | | |
| EP 1392306 | A1 | 20040303 | EP 2002-730462 | 20020605 |
| EP 1392306 | B1 | 20080116 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2005500276 | T | 20050106 | JP 2003-501465 | 20020605 |
| AT 383858 | T | 20080215 | AT 2002-730462 | 20020605 |
| PT 1392306 | E | 20080307 | PT 2002-730462 | 20020605 |
| ES 2296926 | T3 | 20080501 | ES 2002-730462 | 20020605 |
| MX 2003009660 | A | 20040402 | MX 2003-9660 | 20031022 |
| US 20040122047 | A1 | 20040624 | US 2003-715662 | 20031118 |
| US 7211586 | B2 | 20070501 | | |
| PRIORITY APPLN. INFO.: | | | GB 2001-13708 | A 20010606 |
| | | | US 2001-311502P | P 20010810 |
| | | | WO 2002-GB2517 | W 20020605 |
| ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT | | | | |
| OTHER SOURCE(S): | MARPAT 138:24648 | | | |
| GI | | | | |

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AB Title compds. I [R1 represents optionally substituted aryl, optionally substituted heteroaryl, R3NH-Ar1-L2- or R3-NH-C(=O)-NH-Ar2-L2-; R3 represents aryl or heteroaryl; Ar1 represents a saturated, partially saturated

or fully unsatd. 8- to 10-membered bicyclic ring system containing at least one heteroatom selected from O, S or N; Ar2 represents aryldiyl or heteroaryldiyl; L1 represents a linkage, such as an alkylene linkage; L2 represents an alkylene chain linkage; R2 represents hydrogen, halogen, C1-4alkyl or C1-4alkoxy; and Y is carboxy or an acid bioisostere; but excluding compds. where an oxygen, nitrogen or sulfur atom is attached directly to a carbon carbon multiple bond of an alkenylene or alkynylene residue] and the corresponding N-oxides and ester prodrugs thereof, and the pharmaceutically acceptable salts and solvates of such compds., and the N-oxides and ester prodrugs thereof, are prepared and disclosed as antiinflammatory agents. Thus, II was prepared by hydrolysis of 3-(((4-methyl-2-o-tolylaminobenzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-butanoic acid Et ester (preparation given). In adhesion assays, particular compds. of the invention possessed IC50 values in the range of 77 nM to 100 μ M in anal. with both fibronectin and VCAM-1. Such compds. have valuable pharmaceutical properties, in particular the ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4(α 4 β 1).

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L2 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN
 ACCESSION NUMBER: 2002:650984 HCAPLUS

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DOCUMENT NUMBER: 137:337860
TITLE: Potent and Selective Inhibitors of PDGF Receptor Phosphorylation. 2. Synthesis, Structure Activity Relationship, Improvement of Aqueous Solubility, and Biological Effects of 4-[4-(N-Substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline Derivatives
AUTHOR(S): Matsuno, Kenji; Nakajima, Takao; Ichimura, Michio; Giese, Neill A.; Yu, Jin-Chen; Lokker, Nathalie A.; Ushiki, Junko; Ide, Shinichi; Oda, Shoji; Nomoto, Yuji
CORPORATE SOURCE: Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co. Ltd., Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8731, Japan
SOURCE: Journal of Medicinal Chemistry (2002), 45(20), 4513-4523
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:337860
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Structure-activity relationships in 4-[4-(N-substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazolines I (X = O, S; n = 0 - 2; R = Ph, 4-ClC₆H₄, 3-pyridyl, 2-thienyl, etc.), analogs of which are known potent inhibitors of the phosphorylation of platelet derived growth factor receptor (PDGFR), were investigated. It was shown that insertion of the methylene or ethylene unit in ureas I (X = O, n = 1, 2) resulted in decreasing activity compared to N-aryl substituted analogs I (X = O, n = 0), while the opposite tendency was observed with thioureas. Quinazolines I [X = NCN, (NC)2C, O2NCH; n = 1; R = 4-ClC₆H₄, 3,4-(OCH₂O)C₆H₃, etc.], containing cyanoguanidine moiety or related dicyanovinyl or nitrovinyl group as a bioisostere of thiourea, showed low activity. The presence of hydrogen atom on the (thio)urea moiety and stereochem. of the substituent were essential for inhibition of PDGFR phosphorylation. Introduction of a Me group in 5-position of the piperazine ring and enlargement of the piperazine ring reduced inhibitory activity. As the result of this structure optimization, benzylthiourea analogs I (X = S, n = 1) with a small substituent in the 4-position of the substituent Ph ring or with 3,4-methylenedioxy group, e.g. II, were found to be optimal for selective and potent activity. II was also found to inhibit smooth muscle cell proliferation and migration induced by platelet derived growth factor-BB (PDGF-BB) and suppressed neointima formation following balloon injury in rat carotid artery by oral administration. Replacement of the benzyl group in I (X = S, n = 1, R = Ph) with a heterocycle-containing moiety, such as 3-pyridylmethyl or 3-thienyl, improved aqueous solubility without loss of activity and kinase selectivity. Therefore, [(thio)carbamoyl-1-piperazinyl]-6,7-dimethoxyquinazolines I may be expected to have a potential as therapeutic agents for the treatment of restenosis.

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OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS
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REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
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L2 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:251267 HCAPLUS

DOCUMENT NUMBER: 137:279063

TITLE: Synthesis and biological evaluation of aroylguanidines
related to amiloride as inhibitors of the human
platelet Na⁺/H⁺ exchanger

AUTHOR(S): Laeckmann, Didier; Rogister, Francoise; Dejardin,
Jean-Victor; Prosperi-Meys, Christelle; Geczy, Joseph;
Delarge, Jacques; Masereel, Bernard

CORPORATE SOURCE: Natural and Synthetic Drugs Research Center,
Department of Medicinal Chemistry, CHU, Universite de
Liege, Liege, B-4000, Belg.

SOURCE: Bioorganic & Medicinal Chemistry (2002), 10(6),
1793-1804

CODEN: BMECEP; ISSN: 0968-0896

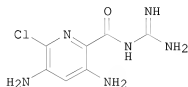
PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

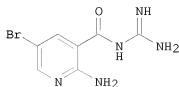
LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:279063

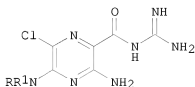
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I



II



III

AB Pyridine and benzene bioisosteres of amiloride such as I and II were synthesized and evaluated for their inhibitory potency against the sodium-hydrogen exchanger involved in intracellular pH regulation. Substituted diaminochloro-2-pyridinecarbonyl and diaminochloro-3-pyridinecarbonyl guanidines are prepared from 2-chloro-6-methyl-3,5-dinitropyridine and 2-methyl-1,5-pentanedinitrile, resp. Dichloro- and trichloropyridine-3-carbonyl guanidines, and simple pyridinecarbonyl and benzoyl guanidines are also prepared. Several benzene derivs. and compds. bearing an carbonylguanidine

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moiety in the meta position of the pyridine nitrogen were much more potent than amiloride, but less so than the pyrazine inhibitor III (R = Et; R1 = Me2CH). II is the most active mol. in assays measuring the reduction in human platelet swelling due to sodium ion uptake and in assays of the inhibition of sodium ion uptake, with IC50 values of 0.8 μ M in both assays. Replacement of the pyrazine ring of amiloride III (R = R1 = H) by a pyridine or a Ph ring improved the inhibitory potency for the sodium-hydrogen exchanger involved in intracellular pH regulation in the order Ph > pyridine > pyrazine.

OS.CITING REF COUNT: 22 THERE ARE 22 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:923773 HCAPLUS
DOCUMENT NUMBER: 136:37607
TITLE: Preparation of benzimidazolyloxobenzazepinylacetates and related compounds as integrin ligands.
INVENTOR(S): Geneste, Herve; Kling, Andreas; Lange, Udo; Lauterbach, Arnulf; Seitz, Werner; Graef, Claudia Isabella; Subkowski, Thomas; Hornberger, Wilfried
PATENT ASSIGNEE(S): Basf Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2001096312 | A1 | 20011220 | WO 2001-EP6779 | 20010615 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG DE 10028575 A1 20020314 DE 2000-10028575 20000614 AU 2001085748 A 20011224 AU 2001-85748 20010615 EP 1289962 A1 20030312 EP 2001-964986 20010615 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR US 20040063934 A1 20040401 US 2003-311369 20030908 US 7279468 B2 20071009 PRIORITY APPLN. INFO.: DE 2000-10028575 A 20000614 WO 2001-EP6779 W 20010615 | | | | |

OTHER SOURCE(S): MARPAT 136:37607
AB BGUT [T = CO2H, group hydrolyzeable to CO2H, bioisostere of CO2H; U = Xa(CR1R2)b, CR1:CR2, C.tplbond.C, CR1; a = 0, 1; b = 0-2; X = CR3R4, NR5, O, S; R1-R4 = H, OH, amino, CONH2, halo, alkyl, alkenyl, alkynyl, etc.; R5 = H, (substituted) alkyl, cycloalkyl, alkoxy carbonyl,

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alkylsulfonyl, etc.; G = optionally condensed azepine or diazepine group;
 B = structural element containing ≥ 1 atom which can function as an
 H-acceptor under physiol. conditions to form hydrogen bonds],
 were prepared as integrin ligands (no data). Title compds. bind to integrin
 receptors, in particular to $\alpha V\beta 3$ integrin receptors. Thus,
 [5-(2-tert-butoxy-2-oxoethyl)-1-oxo-1,3,4,5-tetrahydro-2H-2-benzazepin-2-
 yl]acetic acid (preparation given) and
 N-(4-aminomethylphenyl)-1H-benzimidazole-
 2-amine hydrochloride in DMF at 0° were treated with
 N-methylmorpholine and TOTU followed by stirring for 1 h to give 38%
 tert-Bu [2-[2-[[4-(1H-benzimidazol-2-ylamino)benzyl]amino]-2-oxoethyl]-1-
 oxo-2,3,4,5-tetrahydro-1H-benzazepin-5-yl]acetate. Drug preps. containing
 the title compds. together with numerous other classes of drugs, e.g.,
 endothelin antagonists, ACE inhibitors, caspase inhibitors, etc., are
 claimed.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:903802 HCAPLUS

DOCUMENT NUMBER: 136:37604

TITLE: Preparation of azolylazepinylacetates as ligands of
 integrin receptors.

INVENTOR(S): Geneste, Herve; Kling, Andreas; Lange, Udo; Seitz,
 Werner; Graef, Claudia Isabella; Subkowski, Thomas;
 Hornberger, Wilfried; Lauterbach, Arnulf

PATENT ASSIGNEE(S): BASF AG, Germany

SOURCE: PCT Int. Appl., 187 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|------------------|----------|
| WO 2001093840 | A2 | 20011213 | WO 2001-EP6397 | 20010606 |
| WO 2001093840 | A3 | 20020808 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| DE 10027514 | A1 | 20020103 | DE 2000-10027514 | 20000606 |
| AU 2001067526 | A | 20011217 | AU 2001-67526 | 20010606 |
| CA 2411549 | A1 | 20021205 | CA 2001-2411549 | 20010606 |
| EP 1286673 | A2 | 20030305 | EP 2001-945258 | 20010606 |
| EP 1286673 | B1 | 20050525 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| JP 2004501120 | T | 20040115 | JP 2002-501413 | 20010606 |
| AT 296102 | T | 20050615 | AT 2001-945258 | 20010606 |

Updated Search

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|------------------------|----|----------|------------------|------------|
| MX 2002012015 | A | 20030609 | MX 2002-12015 | 20021205 |
| US 20080221082 | A1 | 20080911 | US 2006-297202 | 20061128 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10027514 | A 20000606 |
| | | | WO 2001-EP6397 | W 20010606 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 136:37604

AB Use of BGL [L = UT; T = CO2H, group hydrolyzable to CO2H, or a CO2H biosostere; U = Xa(CR1R2)b, CR1:CR2, C.tplbond.C, CR1; X = CR3R4, imino, O, S; a = 0, 1; b = 0-2; R1-R4 = H, T, OH, amino, CONH2, halo, (substituted) alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, etc.; G = specified heterocyclylene; B = structural element containing ≥1 atom which under physiol. conditions can undergo hydrogen bridge bonding] as integrin receptor ligands is claimed (no data). Thus, [5-(2-tert-butoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzazepin-1-yl]acetic acid (preparation given) and N-[5-(aminomethyl)thiazol-2-yl]guanidine dihydrochloride (preparation given) in DMF at 0° were treated with N-methylmorpholine and TOTU to give 65% tert-Bu [1-[2-[[[2-[[amino(imino)methyl]amino]thiazol-5-yl]methyl]amino]-2-oxoethyl]-2-oxo-2,3,4,5-tetrahydro-1H-benzazepin-5-yl]acetate. Drug preps. containing BGL and numerous other drug classes, e.g. blood platelet adhesion, activation, and aggregation inhibitors, are also claimed.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2000:708002 HCAPLUS

DOCUMENT NUMBER: 134:29374

TITLE: Synthesis of 2,4-diaminopyrido[2,3-d]pyrimidines and 2,4-diaminoquinazolines with bulky dibenz[b,f]azepine and dibenzo[a,d]-cycloheptene substituents at the 6-position as inhibitors of dihydrofolate reductase from *Pneumocystis carinii*, *Toxoplasma gondii*, and *Mycobacterium avium*

AUTHOR(S): Rosowsky, Andre; Fu, Hongning; Queener, Sherry F.

CORPORATE SOURCE: Dana-Farber Cancer Institute and the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Journal of Heterocyclic Chemistry (2000), 37(4), 921-926

CODEN: JHTCAD; ISSN: 0022-152X

PUBLISHER: HeteroCorporation

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 134:29374

AB The synthesis of four previously undescribed 2,4-diaminopyrido[2,3-d]pyrimidines and 2,4-diaminoquinazolines with a bulky tricyclic aromatic group at the 6-position is described. Condensation of dibenz[b,f]azepine with 2,4-diamino-6-bromomethylpyrido[2,3-d]pyrimidine and 2,4-diamino-6-bromomethylquinazoline in the presence of sodium hydride afforded N-[(2,4-diaminopyrido[2,3-d]-pyrimidin-6-yl)methyl]dibenz[b,f]azepine and N-[(2,4-diaminoquinazolin-6-yl)methyl]dibenz[b,f]azepine, resp. Condensation of 5-chlorodibenz[a,d]cycloheptene and

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5-chloro-10,11-dihydrodibenzo[a,d]cycloheptene with 2,4,6-triaminoquinazoline (13) afforded 5-[(2,4-diaminoquinazolin-6-yl)amino]-5H-dibenzo[a,d]cycloheptene and the corresponding 10,11-dihydro derivative, resp. The bromides, as hydrobromic acid salts, were obtained from the corresponding nitriles according to a standard three-step sequence consisting of treatment with Raney nickel in formic acid followed by reduction with sodium borohydride and bromination with dry hydrogen bromide in glacial acetic acid. The title compds. were evaluated in vitro for the ability to inhibit dihydrofolate reductase from *Pneumocystis carinii*, *Toxoplasma gondii*, *Mycobacterium avium*, and rat liver. They were potent inhibitors of all four enzymes, with IC50 values in the 0.03-0.1 μ M range. However the selectivity of these compds. for the parasite enzymes relative to the rat enzyme was <10-fold, whereas the recently reported lead compound in this series, N-[(2,4-diaminopteridin-6-yl)methyl]dibenz[b,f]azepine has >100-fold selectivity for the *T. gondii* and *M. avium* enzyme and 21-fold selectivity for the *P. carinii* enzyme.

OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1999:383503 HCAPLUS

DOCUMENT NUMBER: 131:228859

TITLE: Synthesis and muscarinic receptor pharmacology of a series of 4,5,6,7-tetrahydroisothiazolo[4,5-c]pyridine bioisosteres of arecoline

AUTHOR(S): Pedersen, Henrik; Brauner-Osborne, Hans; Ball, Richard G.; Frydenvang, Karla; Meier, Eddi; Bogeso, Klaus P.; Krogsgaard-Larsen, Povl

CORPORATE SOURCE: Medicinal Chemistry Research, Valby-Copenhagen, DK-2500, Den.

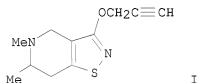
SOURCE: Bioorganic & Medicinal Chemistry (1999), 7(5), 795-809
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

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AB 7 Series of O- and ring-alkylated derivs. of 4,5,6,7-tetrahydroisothiazolo[4,5-c]pyridin-3-ol, e.g. 1, was synthesized via treatment of appropriately substituted 4-benzylamino-1,2,5,6-tetrahydropyridine-3-carboxamides with hydrogen sulfide and subsequent ring closure by oxidation with bromine. The muscarinic receptor affinity as well as estimated relative

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efficacy and subtype selectivity of this series of bicyclic arecoline bioisosteres were determined using rat brain membranes and a number of tritiated muscarinic receptor ligands. The effects at the five cloned human muscarinic receptor subtypes of a selected series of chiral analogs, with established absolute stereochem., were studied using receptor selection and amplification technol. (R-SAT). The potency, relative efficacy, and receptor subtype selectivity of these compds. were related to the structure of the O-substituents and the position and stereochem. orientation of the piperidine ring Me substituents.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1998:597933 HCAPLUS

DOCUMENT NUMBER: 130:25303

TITLE: The synthesis of 1,2,4-oxadiazoles from carboxyl group of amino acids and dipeptides

AUTHOR(S): Sollner, Marija; Levacic, Suzana; Pecar, Slavko

CORPORATE SOURCE: Faculty of Pharmacy, University of Ljubljana, Ljubljana, 1000, Slovenia

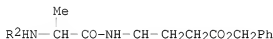
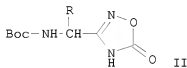
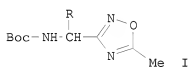
SOURCE: Peptides 1996, Proceedings of the European Peptide Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998), Meeting Date 1996, 809-810. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.

CODEN: 66RCA5

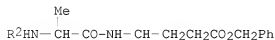
DOCUMENT TYPE: Conference

LANGUAGE: English

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IV

Updated Search

AB Peptides represent a large class of bioactive substances. However, they are limited in their potential for treating a variety of diseases because of their pharmacokinetic properties. In order to improve their oral bioavailability and chemical stability, peptide bonds and amino acid moieties in peptides have been replaced with different structural fragments. Recently, the different five- or six-membered heterocycles, especially 1,2,4-oxadiazoles, were reported as peptidomimetics as well as ester and amide bioisosteres. These findings prompted the author's interest to find an easy and convenient synthesis of 1,2,4-oxadiazoles and 5-oxo-1,2,4-oxadiazoles from the carboxyl group of amino acids and dipeptides. The basic syntheses for the preparation of the 1,2,4-oxadiazoles are usually amidoximes. In this study, the authors converted carboxyl group of Boc-L-amino acids BocNHCHRCO₂H (R = Me, iso-Pr) or dipeptide first into amides BocNHCHRCONH₂ and BocNHCHMeCONHCH(CONH₂)CH₂CH₂CO₂CH₂Ph. The amidoximes BocNHCHRC(:NOH)NH₂ BocNHCHMeCONHCH[C(:NOH)NH₂]CH₂CH₂CO₂CH₂Ph were synthesized from corresponding nitriles BocNHCHRCN and BocNHCHMeCONHCH(CN)CH₂CH₂CO₂CH₂Ph according to the general method in 70-80 % yield. After treatment of the amidoximes with chloroformates or acetyl chloride in the presence of triethylamine the acylamidoximes BocNHCHRC(:NOR1)NH₂ and BocNHCHMeCONHCH[C(:NOR1)NH₂]CH₂CH₂CO₂CH₂Ph (R₁ = Ac, CO₂Me, CO₂Et) were obtained. Cyclization of the latter acylamidoximes by heat in an inert atmosphere provided the 1,2,4-oxadiazole derivs. (I and II; R = Me, iso-Pr) and (III and IV ; R₂ = Boc) in good yields (70-80 %), without the use of base to promote the cyclization. The removal of the Boc-protecting group under standard conditions did not affect the 1,2,4-oxadiazole fragments. The corresponding salts III.HCl and IV.HCl (R₂ = H) are stable, but very hygroscopic compds. The synthesized 1,2,4-oxadiazoles can be useful building moieties in the design and synthesis of modified bioactive peptides, especially when the hydrogen acceptor character of the amide or carboxyl group of the native protein is essential for the bioactivity.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1997:637201 HCAPLUS

DOCUMENT NUMBER: 127:318585

ORIGINAL REFERENCE NO.: 127:62433a,62436a

TITLE: Structural characteristics of isoxazol-3-ol and isothiazol-3-ol, carboxy group bioisosteres examined by x-ray crystallography and ab initio calculations

AUTHOR(S): Frydenvang, Karla; Matzen, Lisa; Norrby, Per-Ola; Slok, Frank A.; Liljefors, Tommy; Krosgaard-Larsen, Povl; Jaroszewski, Jerzy W.

CORPORATE SOURCE: PharmaBiotec Research Center, Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Universitetsparken, Copenhagen, DK-2100, Den.

SOURCE: Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry (1997), (9), 1783-1791 CODEN: JCPKBH; ISSN: 0300-9580

PUBLISHER: Royal Society of Chemistry

DOCUMENT TYPE: Journal

stn

LANGUAGE: English

AB Low-temperature single-crystal structure detns. have been carried out on isoxazol-3-ol, 5-methyl-isoxazol-3-ol, isothiazol-3-ol and 5-methylisothiazol-3-ol, the heterocyclic ring systems used as carboxy group bioisosteres in numerous neuroactive analogs of 4-aminobutyric acid (GABA) and glutamic acid. All compds. form hydrogen-bonded dimers in the solid state. The OH...N hydrogen bonds are shorter in isoxazol-3-ols than in isothiazol-3-ols. The excess mol. van der Waals volume of the sulfur-containing ring systems as compared to the corresponding isoxazol-3-ols amts. to about 15%. The sulfur substitution significantly affects the position of the 5-substituents in relation to the heterocyclic ring. Such effects may contribute to the observed differences in pharmacol. effects of the structurally related isoxazol-3-ol and isothiazol-3-ol amino acids. The geometries of the compds. have been optimized by ab initio calcns. at the HF/6-31G* level, and in some cases also at the MP2/6-311G** level. The gas-phase calcns. are in agreement with the exptl. data, especially when correction for the effects of hydrogen bonding is made, as estimated using a complex between isoxazol-3-ol and formic acid. Calculated dipole moments of isoxazol-3-ols and isothiazol-3-ols are similar. Isoxazol-3-ol is more acidic than isothiazol-3-ol by 1.7 pKa unit as determined by ¹³C NMR titration, and the differences in acidity are believed to be one of the major factors causing the differences in the biol. actions of isoxazol-3-ol amino acids and the corresponding isothiazol-3-ol analogs.

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1997:526723 HCAPLUS

DOCUMENT NUMBER: 127:185378

ORIGINAL REFERENCE NO.: 127:35765a,35768a

TITLE: Heteroaryl Analogs of AMPA. Synthesis and Quantitative

Structure-Activity Relationships

AUTHOR(S): Bang-Andersen, Benny; Lenz, Sibylle M.; Skjaerbaek,

Niels; Soby, Karina K.; Hansen, Hans O.; Ebert,

Bjarke; Bogeso, Klaus P.; Krogsgaard-Larsen, Povl

CORPORATE SOURCE: Research Departments, H. Lundbeck A/S, Valby, DK-2500, Den.

SOURCE: Journal of Medicinal Chemistry (1997), 40(18), 2831-2842

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A number of 3-isoxazolol bioisosteres of (S)-glutamic acid (Glu), in which the Me group of (RS)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) was replaced by different 5-membered heterocyclic rings, were synthesized. Comparative in vitro pharmacol. studies on this series of AMPA analogs were performed using receptor binding assays (IC₅₀ values) and the electrophysiol. rat cortical slice model (EC₅₀ values). None of these compds. showed detectable affinity for the N-methyl-D-aspartic acid subtype of Glu receptors. Some of the compds. were weak inhibitors

of [3H]kainic acid binding. The inhibitory effects on [3H]AMPA binding and agonist potencies at AMPA receptors of the Glu 3-isoxazolol bioisosteres were strictly dependent on the structure, electrostatic potential, and Me substitution of the heterocyclic 5-substituent. Thus, while (RS)-2-Amino-3-[3-hydroxy-5-(thiazol-2-yl)isoxazol-4-yl]propionic Acid (IC50 = 0.094 μ M; EC50 = 2.3 μ M) was approx. equipotent with AMPA (IC50 = 0.023 μ M; EC50 = 5.4 μ M), (RS)-2-amino-3-[3-hydroxy-5-(1H-imidazol-2-yl)isoxazol-4-yl]propionic acid (IC50 = 48 μ M; EC50 = 550 μ M) was some 2 orders of magnitude weaker than AMPA, and (RS)-2-amino-3-[3-hydroxy-5-(1-methyl-1H-imidazol-2-yl)isoxazol-4-yl]propionic acid (IC50 > 100 μ M; EC50 > 1000 μ M) was inactive. Furthermore, (RS)-2-amino-3-[3-hydroxy-5-(2-methyl-2H-tetrazol-5-yl)isoxazol-4-yl]propionic acid (IC50 = 0.030 μ M; EC50 = 0.92 μ M) was more potent than AMPA, whereas its N-1 Me isomer, (RS)-2-amino-3-[3-hydroxy-5-(1-methyl-1H-tetrazol-5-yl)isoxazol-4-yl]propionic acid (IC50 = 54 μ M; EC50 > 1000 μ M) was inactive as an AMPA agonist. A quant. structure-activity relationship (QSAR) anal. revealed a pos. correlation between receptor affinity, electrostatic potential near the nitrogen atom at the "ortho" position of the heterocyclic 5-substituent, and the rotational energy barrier around the bond connecting the two rings. We envisage that a hydrogen bond between the protonated amino group and an ortho-positioned heteroatom of the ring substituent at the 5-position stabilize receptor-active conformations of these AMPA analogs.

OS.CITING REF COUNT: 39 THERE ARE 39 CAPLUS RECORDS THAT CITE THIS RECORD (39 CITINGS)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1996:528310 HCAPLUS

DOCUMENT NUMBER: 125:274989

ORIGINAL REFERENCE NO.: 125:51421a,51424a

TITLE: Synthesis and conformational study of β -hydroxy sulfones, bioisosteres of oxisuran metabolites, and their O-methyl derivatives

AUTHOR(S): Alvarez-Ibarra, C.; Cuervo-Rodriguez, R.; Fernandez-Monreal, M. C.; Ruiz, M. P.

CORPORATE SOURCE: Dep. Quimica Organica I, Ciudad Univ., Madrid, 28040, Spain

SOURCE: Tetrahedron (1996), 52(34), 11239-11256
CODEN: TETRAB; ISSN: 0040-4020

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The synthesis and conformational anal. of 2-(methylsulfonyl)-1-(2-quinolyl)ethanol, 2-(methylsulfonyl)-1-(1-isoquinolyl)ethanol, 2-(methylsulfonyl)-1-(2-pyrazinyl)ethanol, and the O-Me derivs., 2-(methylsulfonyl)-1-(methoxy)-1-(2-quinolyl)ethane and 2-(methylsulfonyl)-1-(methoxy)-1-(1-isoquinolyl)ethane, are reported. The conformational anal. of β -hydroxy sulfones and β -methoxy sulfones has been carried out from the observed vicinal coupling consts., using a mol. mechanics force field (MMX) and the Altona relationship as fundamental tools. Polar interactions are the main factor that control the stability of the different conformations, with steric effects and

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intramol. hydrogen bonding less important contributions.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD
(3 CITINGS)

L2 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1995:352125 HCAPLUS

DOCUMENT NUMBER: 123:169535

ORIGINAL REFERENCE NO.: 123:30267a,30270a

TITLE: Studies on New Acidic Azoles as Glucose-Lowering

Agents in Obese, Diabetic db/db Mice

AUTHOR(S): Kees, Kenneth L.; Caggiano, Thomas J.; Steiner, Kurt

E.; Fitzgerald, John J., Jr.; Kates, Michael J.;

Christos, Thomas E.; Kulishoff, John M.; Moore, Robin

D.; McCaleb, Michael L.

CORPORATE SOURCE: Wyeth-Ayerst Research, Princeton, NJ, 08543-8000, USA

SOURCE: Journal of Medicinal Chemistry (1995), 38(4), 617-28

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 123:169535

AB Bioisosteric substitution was used as a tool to generate several new structural alternatives to the thiazolidine-2,4-dione and tetrazole heterocycles as potential antidiabetic agents. Among the initial leads that emerged from this strategy, a family of acidic azoles, isoxazol-3- and -5-ones and a pyrazol-3-one, showed significant plasma glucose-lowering activity (17-42% reduction) in genetically obese, diabetic db/db mice at a dose of 100 mg/kg/day +4. Structure-activity relationship studies determined that 5-alkyl-4-(arylmethyl)pyrazol-3-ones, which exist in solution as aromatic enol/iminol tautomers, were the most promising new class of potential antidiabetic agent (32-45% reduction at 20 mg/kg/d +4). Included in this work are convenient syntheses for several types of acidic azoles that may find use as new acidic bioisosteres in medicinal chemical such as the antidiabetic lead 5-(trifluoromethyl)pyrazol-3-one, hydroxy tautomer, and aza homologs of the pyrazolones, 1,2,3-triazol-5-ones (hydroxy tautomer) and 1,2,3,4-tetrazol-5-one heterocycles. Log P and pKa data for 15 potential acidic bioisosteres, all appended to a 2-naphthalenylmethyl residue so as to maintain a similar distance between the acidic hydrogen and arene nucleus, are presented. This new data set allows comparison of a wide variety of potential acid mimetics (pKa 3.78-10.66; log P -0.21 to 2.76) for future drug design.

OS.CITING REF COUNT: 28 THERE ARE 28 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)

L2 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1994:680457 HCAPLUS

DOCUMENT NUMBER: 121:280457

ORIGINAL REFERENCE NO.: 121:51199a,51202a

TITLE: Synthesis, Configurational Assignment and Conformational Analysis of β -Hydroxy Sulfoxides, Bioisosteres of Oxisuran Metabolites, and their O-Methyl Derivatives

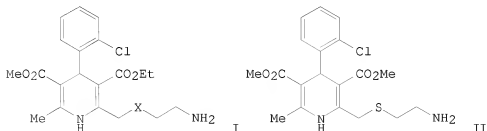
AUTHOR(S): Alvarez-Ibarra, C.; Cuervo-Rodriguez, R.;

Fernandez-Monreal, M. C.; Ruiz, M. P.

CORPORATE SOURCE: Facultad de Quimica, Universidad Complutense, Madrid,

stn

28040, Spain
SOURCE: Journal of Organic Chemistry (1994), 59(24), 7284-91
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Synthesis, configurational assignment, and conformational anal. of diastereoisomers of 2-(methylsulfinyl)-1-(2-quinolyl)ethanol, 2-(methylsulfinyl)-1-(1-isoquinolyl)ethanol, 2-(methylsulfinyl)-1-(2-pyrazinyl)ethanol, and their O-Me derivs. are reported. The configurational assignment and conformational anal. of the two diastereoisomers of β -hydroxy sulfoxides and β -methoxy sulfoxides have been carried out from the observed vicinal coupling consts. using the mol. mechanics force field (MMX) and the Altona relationship as fundamental tools. The conformational equilibrium is explained in terms of polar and steric factors. Of significant importance was the role of intramol. hydrogen bonding in the RS/SR isomers of β -hydroxy sulfoxides.
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)
L2 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1993:237 HCAPLUS
DOCUMENT NUMBER: 118:237
ORIGINAL REFERENCE NO.: 118:39a,42a
TITLE: Long-acting dihydropyridine calcium antagonists. Part 8. A comparison of the pharmacological and pharmacokinetic properties of amlodipine with its carba and thio-bioisosteres
AUTHOR(S): Alker, David; Burges, Roger A.; Campbell, Simon F.; Carter, Anthony J.; Cross, Peter E.; Gardiner, Donald G.; Humphrey, Michael J.; Stopher, David A.
CORPORATE SOURCE: Dep. Chem., Pfizer Cent. Res., Sandwich/Kent, CT13 9NJ, UK
SOURCE: Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry (1972-1999) (1992), (7), 1137-40
CODEN: JCPKBH; ISSN: 0300-9580
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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AB In order to evaluate the contribution to the overall pharmacokinetic and pharmacol. profile of amlodipine (I, X=O) made by the side-chain ether oxygen atom and the intramol. hydrogen bond to the DHP ring NH proton, the profile of amlodipine was compared with that of its carba and thio bioisosteres. Replacing the side-chain oxygen by carbon dramatically reduces in vitro calcium antagonist potency, an effect which may be attributed to the loss of a through-bond inductive effect on the DHP ring NH proton, while both the thio and carba analogs show lower in vitro selectivity than amlodipine for vascular over cardiac tissue. On i.v. administration to anesthetized dogs, compds. 2 I (X = S) and 3 I (X = CH₂) both exhibit marked depression of myocardial contractility at doses equal or close to their ED₅₀ for reduction of coronary vascular resistance. The plasma clearances of amlodipine and analogs 3 and 4 (II) are similar, suggesting that the conformation adopted by the 2-sidechain has little influence on this parameter although bulk and polarity are important. However, compds. 3 and 4 have markedly lower vols. of distribution (6 and 8 dm³ kg⁻¹, resp.) than amlodipine (25 dm³ kg⁻¹) and consequently shorter half-lives; this may be a consequence of their inability to form an intramol. hydrogen bond.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L2 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1992:644998 HCAPLUS

DOCUMENT NUMBER: 117:244998

ORIGINAL REFERENCE NO.: 117:42171a, 42174a

TITLE: Steric and electronic requirements for muscarinic receptor-stimulated phosphoinositide turnover in the CNS in a series of arecoline bioisosteres

AUTHOR(S): Ngur, Dan; Rohnich, Scott; Mitch, Charles H.; Quimby, Steven J.; Ward, John S.; Merritt, Leander; Sauerberg, Per; Messer, William S., Jr.; Hoss, Wayne

CORPORATE SOURCE: Coll. Pharm., Univ. Toledo, Toledo, OH, 43606, USA

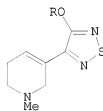
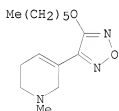
SOURCE: Biochemical and Biophysical Research Communications (1992), 187(3), 1389-94

CODEN: BBRCA9; ISSN: 0006-291X

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB A series of arecoline derivs. was utilized to assess steric and electronic effects important for activating muscarinic receptors in the central nervous system (CNS). Arecoline derivs. in which the Me ester moiety was replaced by hexyloxy-1,2,5-oxadiazole (I), hexyloxythiophene

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(II), or hexyloxypyrazine (III) were compared with the hexyloxy-1,2,5-thiadiazole compound (IV) known from previous work to be active as an M1/M3 partial agonist. MNDO calcns. showed that the N-S bonds of the alkoxythiadiazole ring were highly polarized with the ability to form H-bonds to the N's. On the other hand, the smaller oxadiazole had lower polarities in the N-O bonds and reduced ability to form H-bonds, the thiophene was of comparable size to the thiadiazole and had large C-S bond polarities without the H-bond capability and the pyrazine had limited ability to form H-bonds. The compds. were compared with respect to their abilities to stimulate phosphoinositide (PI) turnover in the hippocampus of the rat brain. IV was more active than I-III for stimulating the PI turnover response. The data suggest that the ability to form H-bonds is an important factor for the ability of the arecoline derivative (V) to stimulate M1 muscarinic receptors in the CNS.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L2 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1992:255864 HCAPLUS

DOCUMENT NUMBER: 116:255864

ORIGINAL REFERENCE NO.: 116:43399a,43402a

TITLE: Antiandrogenic steroidal sulfonyl heterocycles.
Utility of electrostatic complementarity in defining
bioisosteric sulfonyl heterocycles

AUTHOR(S): Mallamo, John P.; Pilling, Garry M.; Wetzel, Joseph
R.; Kowalczyk, Paul J.; Bell, Malcolm R.; Kullnig,
Rudolph K.; Batzold, Frederick H.; Juniewicz, Paul E.;
Winneker, Richard C.; Luss, Henry R.
CORPORATE SOURCE: Res. Div., Sterling Winthrop Pharm., Rensselaer, NY,
12144, USA

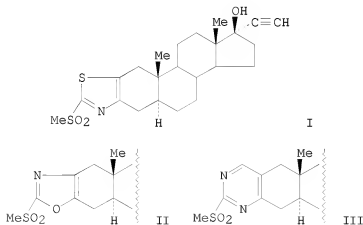
SOURCE: Journal of Medicinal Chemistry (1992), 35(10), 1663-70
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 116:255864

GI



Updated Search

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AB Complementarity of electrostatic potential surface maps was utilized in defining bioisosteric steroidal androgen receptor antagonists. Semiempirical and ab initio level calcs. performed on a series of methanesulfonyl heterocycles indicated the requirement for a partial neg. charge at the heteroatom attached to C-3 of the steroid nucleus to attain androgen receptor affinity. Synthesis and testing of six heterocycle A-ring-fused dihydroethisterone derivs., e.g., I-III, support this hypothesis, and two new androgen receptor antagonists of this class, I and II, have been identified.

OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)

L2 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1990:511694 HCAPLUS

DOCUMENT NUMBER: 113:111694

ORIGINAL REFERENCE NO.: 113:18841a,18844a

TITLE: S-[2-[(2'-carbamoylethyl)amino]ethyl] phosphorothioate and related compounds as potential antiradiation agents

AUTHOR(S): Carroll, F. Ivy; Gopinathan, M. B.; Philip, Abraham
CORPORATE SOURCE: Research Triangle Inst., Research Triangle Park, NC, 27709, USA

SOURCE: Journal of Medicinal Chemistry (1990), 33(9), 2501-8
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A reinvestigation of the radiation protection activity of S-[2-[(2'-carbamylethyl)amino]ethyl]lithium hydrogen phosphorothioate (I) revealed that this compound possessed good (70% protection at a dose of 600 mg/kg) activity in γ -irradiated mice. The thione and imino bioisosteres of I, S-[2-(2'-thiocarbamylethylamino)ethyl]lithium hydrogen phosphorothioate (II) and S-[2-(2'-aminodinoethylamino)-ethyl]phosphorothioic acid (III) showed 100% protection at doses of 300 and 150 mg/kg, resp. The N-Me and tert-Bu analogs of amide I, the N-Me analog of the thioamide II, the N-Me analog of amide III, and the cyclic amidine S-[2-[(2'-(4,5-dihydroimidazolyl)ethyl)amino]ethyl]lithium hydrogen phosphorothioate all showed 80% protection at the highest dose tested.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L2 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1990:452065 HCAPLUS

DOCUMENT NUMBER: 113:52065

ORIGINAL REFERENCE NO.: 113:8633a,8636a

TITLE: Synthesis and biological evaluation of new antimuscarinic compounds with amidine basic centers. A useful bioisosteric replacement of classical cationic heads

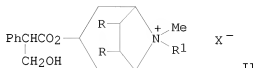
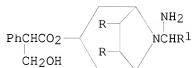
AUTHOR(S): Cereda, Enzo; Ezhaya, Antoine; Gil Quintero, Myrna; Bellora, Elío; Dubini, Enrica; Micheletti, Rosella; Schiavone, Antonio; Brambilla, Alessandro; Schiavi, Giovanni Battista; Donetti, Arturo

CORPORATE SOURCE: Dep. Med. Chem., Ist. De Angeli, Milan, I-20139, Italy

Updated Search

stn

SOURCE: Journal of Medicinal Chemistry (1990), 33(8), 2108-13
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB Amidines (guanidine, formamidine, and acetmidine) were introduced as substitutes for the cationic heads present in atropine, scopolamine and corresponding quaternary derivs. Amidine systems are intermediate in structure between tertiary amines and quaternary compds., at least as regards ionization and electronic properties, but differ from the latter in shape (planar not tetrahedral). They have addnl. binding opportunities on account of their hydrogen-bond-forming capacity. The effect of the introduction of these cationic heads on the affinity for different muscarinic acetylcholine receptor (m-Ac-ChR) subtypes was investigated in vitro, in binding displacement studies, and in functional tests on isolated organs. All new compds (I, R = H or RR = O, R1 = H, Me or NH2), showed high affinity for the m-AcChR considered, comparable or slightly inferior to that of the parent drugs (II, R = H or RR = O, R1 = H, Me or Bu). The new amidine derivs. proved effective as spasmolytic agents with little tendency to cause central effects. However, no separation was achieved of spasmolytic and other untoward effects, like inhibition of salivation. Thus, amidine moieties are effective bioisosteric substitutes for conventional cationic heads present in antimuscarinic agents. Their unusual physicochem. properties make them useful tools when modulation of pharmacokinetic or pharmacodynamic effects is required.

OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)

=> d his

(FILE 'HOME' ENTERED AT 14:01:19 ON 08 MAY 2010)

FILE 'REGISTRY' ENTERED AT 14:01:29 ON 08 MAY 2010

FILE 'HCAPLUS' ENTERED AT 14:01:36 ON 08 MAY 2010

L1 690 S BIOISOSTERE?
L2 21 S L1 AND METHYL AND HYDROGEN
L3 0 S L2 AND REVIEW/DT

=> s l1 and review/dt
2374978 REVIEW/DT

L4 50 L1 AND REVIEW/DT

=> s l4 and methyl

Updated Search

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1144383 METHYL
      767 METHYLS
1144838 METHYL
      (METHYL OR METHYLS)
1032231 ME
      12150 MES
1040139 ME
      (ME OR MES)
1805973 METHYL
      (METHYL OR ME)
L5          3 L4 AND METHYL
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=> d l5, ibib abs, 1-3
'L-3' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'

The following are valid formats:

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ABS ----- GI and AB
ALL ----- BIB, AB, IND, RE
APPS ----- AI, PRAI
BIB ----- AN, plus Bibliographic Data and PI table (default)
CAN ----- List of CA abstract numbers without answer numbers
CBIB ----- AN, plus Compressed Bibliographic Data
CLASS ----- IPC, NCL, ECLA, FTERM
DALL ----- ALL, delimited (end of each field identified)
DMAX ----- MAX, delimited for post-processing
FAM ----- AN, PI and PRAI in table, plus Patent Family data
FBIB ----- AN, BIB, plus Patent FAM
IND ----- Indexing data
IPC ----- International Patent Classifications
MAX ----- ALL, plus Patent FAM, RE
PATS ----- PI, SO
SAM ----- CC, SX, TI, ST, IT
SCAN ----- CC, SX, TI, ST, IT (random display, no answer numbers;
      SCAN must be entered on the same line as the DISPLAY,
      e.g., D SCAN or DISPLAY SCAN)
STD ----- BIB, CLASS

IABS ----- ABS, indented with text labels
IALL ----- ALL, indented with text labels
IBIB ----- BIB, indented with text labels
IMAX ----- MAX, indented with text labels
ISTD ----- STD, indented with text labels

OBIB ----- AN, plus Bibliographic Data (original)
OIBIB ----- OBIB, indented with text labels

SBIB ----- BIB, no citations
SIBIB ----- IBIB, no citations

HIT ----- Fields containing hit terms
HITIND ----- IC, ICA, ICI, NCL, CC and index field (ST and IT)
      containing hit terms
HITRN ----- HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
      its structure diagram
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Updated Search

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HITSEQ ----- HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
KWIC ----- Hit term plus 20 words on either side
OCC ----- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field
codes. For a list of the display field codes, enter HELP DFIELDS at
an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST;
TI,IND; TI,SO. You may specify the format fields in any order and the
information will be displayed in the same order as the format
specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR,
FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC
to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):end

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(FILE 'HOME' ENTERED AT 14:01:19 ON 08 MAY 2010)

FILE 'REGISTRY' ENTERED AT 14:01:29 ON 08 MAY 2010

FILE 'HCAPLUS' ENTERED AT 14:01:36 ON 08 MAY 2010

L1 690 S BIOISOSTERE?
L2 21 S L1 AND METHYL AND HYDROGEN
L3 0 S L2 AND REVIEW/DT
L4 50 S L1 AND REVIEW/DT
L5 3 S L4 AND METHYL

=> d l5, ibib abs, 1-3

THE ESTIMATED COST FOR THIS REQUEST IS 9.30 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

L5 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2010 ACS ON STN

ACCESSION NUMBER: 2008:967263 HCAPLUS

DOCUMENT NUMBER: 149:190846

TITLE: Melatonin receptor agonists: SAR and applications to
the treatment of sleep-wake disorders

AUTHOR(S): Rivara, Silvia; Mor, Marco; Bedini, Annalida; Spadoni,
Gilberto; Tarzia, Giorgio

CORPORATE SOURCE: Dipartimento Farmaceutico, Universita degli Studi di
Parma, Parma, 43100, Italy

SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United
Arab Emirates) (2008), 8(11), 954-968

CODEN: CTMCCL; ISSN: 1568-0266

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Melatonin (N-acetyl-5-methoxytryptamine) is synthesized and
released by the pineal gland following a circadian rhythm characterized by
high levels during the night. It shows several pharmacol. effects on

diverse cellular and animal models, mainly related to either its antioxidant activity or to its ability to activate specific receptors (MTr). Melatonin is widely used as a self-administered food additive, but its therapeutic potential needs more investigation and is hampered by its poor pharmacokinetics. This review will focus on the medicinal chemical of agonist ligands of the two human GPCRs MT1 and MT2 melatonin receptors. The recent introduction of ramelteon, a non-selective MT1/MT2 agonist for the treatment of insomnia, and the advancement to clin. trials of other MTr agonists have renewed interest for different classes of compds. endowed with this activity. Several chemical classes of MTr agonists are described in the literature, generally characterized by an indole, or an indole bioisostere, carrying an amide side chain and a methoxy group, or substituents with similar stereoelectronic features. Abundant information is available for non-selective MT1/MT2 ligands, and several mol. models, both ligand- and receptor-based, have been proposed to rationalize their structure activity relationships. Fewer classes of selective agonists have been reported in the literature, and they could help clarifying the physiol. role of the two receptor subtypes. A brief discussion on the therapeutic potential of this class of compds. is based on the clin. data available for the agonists ramelteon, agomelatine, β -methyl-6-chloromelatonin (TIK-301) and VEC-162.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD
(2 CITINGS)
REFERENCE COUNT: 162 THERE ARE 162 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2010 ACS ON STN

ACCESSION NUMBER: 1999:23966 HCAPLUS

DOCUMENT NUMBER: 130:332046

TITLE: Heterocycles as bioisosteres for the
 α -carboxylate moiety of glutamate in AMPA
receptor agonists: a review and theoretical study
AUTHOR(S): Greenwood, Jeremy R.; Vaccarella, Graziano; Capper,
Hugh R.; Allan, Robin D.; Johnston, Graham A. R.
CORPORATE SOURCE: Adrien Albert Laboratory of Medicinal Chemistry,
Department of Pharmacology, University of Sydney,
2006, Australia
SOURCE: Internet Journal of Chemistry [Electronic Publication]
(1998), 1, No pp. Given, ARTICLE No. 38
CODEN: IJCHFJ
URL: <http://www.ijc.com/articles/1998v1/38/abstract.pdf>

PUBLISHER: Internet Journal of Chemistry
DOCUMENT TYPE: Journal; General Review; (online computer
file)

LANGUAGE: English

AB A review with 95 refs. (S)-2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) is the prototypical selective agonist for the AMPA subtype of excitatory amino acid (glutamate) receptors. Several 3-hydroxyisoxazole analogs are known to have activity at this receptor, as do a number of other alanine-substituted heterocyclic phenols, the acidic heterocycles being bioisosteres for the α -carboxylate moiety of glutamate. The increasingly diverse range of known AMPA agonists is reviewed, including a number of novel pyridazine-based analogs. By removal of a common glycine unit, the parent heterocycles

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3-hydroxy-4,5-dimethylisoxazole, 3-hydroxy-4,5-dimethylisothiazole, 4-methyl-5-isoxazolone, 3-hydroxy-4-methyl-1,2,5-thiadiazole, 2-methyl-3,5-dioxo-1,2,4-oxadiazolidine, 1-methyluracil, 6-aza-1-methyluracil, and 3-hydroxy-4-methylpyridazine 1-oxide are modeled as representative of the known α -carboxylate bioisosteres. In addition heterocyclic fragments of inactive hydantoin and 3,5-dioxotriazole quisqualate analogs, and pyridazinone fragments with derivs. of varying potency are considered. These structures and their conjugate bases are subjected to high level ab initio calcs. up to G2(MP2) theory, and semiempirical aqueous phase calcs. using the AM1-SM2 model. Their tautomerism and aqueous pKa behavior are studied in detail, and compared with exptl. data. Mol. geometries and electrostatic potential-derived charge distributions are presented. Electrostatic properties at the Van der Waals surface are compared. Calculated properties are discussed with respect to structural requirements for AMPA receptor activity. Tridentate models of AMPA receptor binding are presented.

L5 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2010 ACS ON STN

ACCESSION NUMBER: 1990:490746 HCAPLUS

DOCUMENT NUMBER: 113:90746

ORIGINAL REFERENCE NO.: 113:15079a,15082a

TITLE: Acidic isostere design: synthetic strategies and recent progress in understanding electronic properties and metabolic stability

AUTHOR(S): Lipinski, Christopher A.; Chenard, Bert L.

CORPORATE SOURCE: Pfizer Cent. Res., Groton, CT, 06340, USA

SOURCE: Pesticide Science (1990), 29(2), 227-40

CODEN: PSSCBG; ISSN: 0031-613X

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 34 refs. The efficient synthesis of a family of twelve acidic heterocycles (mercaptoazoles) of varying acidity from a single common intermediate facilitates the search for new acidic bioisosteres. An extension of this chemical approach led to a new family of phosphonate replacements in prototypes related to the N-methyl-D-aspartate (NMDA) antagonist 2-amino-7-phosphonheptanoic acid (AP7). Acidic isostere design may be facilitated by grouping hydroxylic heterocyclic carboxylic isosteres into one of two electronic classes based on the Gandour hypothesis. The limitations of normal hydroxamic acids as carboxylic acid surrogates suggest that the excellent metabolic stability of reverse hydroxamic acids may be useful in prospective acidic isostere design.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

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(FILE 'HOME' ENTERED AT 14:01:19 ON 08 MAY 2010)

FILE 'REGISTRY' ENTERED AT 14:01:29 ON 08 MAY 2010

FILE 'HCAPLUS' ENTERED AT 14:01:36 ON 08 MAY 2010

L1 690 S BIOISOSTERE?

L2 21 S L1 AND METHYL AND HYDROGEN

L3 0 S L2 AND REVIEW/DT

Updated Search

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L4 50 S L1 AND REVIEW/DT
L5 3 S L4 AND METHYL

=> s 14 and pd < october 2003
23922749 PD < OCTOBER 2003
(PD<20031000)

L6 34 L4 AND PD < OCTOBER 2003

=> d 16, ibib abs, 1-34
THE ESTIMATED COST FOR THIS REQUEST IS 105.40 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

L6 ANSWER 1 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2004:841444 HCAPLUS
DOCUMENT NUMBER: 142:387969
TITLE: Inhibitors of aminoacyl-tRNA synthetases as
antibiotics and tools for structural and mechanistic
studies

AUTHOR(S): Chenevert, Robert; Bernier, Stephane; Lapointe,
Jacques
CORPORATE SOURCE: Departement de Chimie, Universite Laval, QC, Can.
SOURCE: Translation Mechanisms (2003), 416-428.
Editor(s): Lapointe, Jacques; Brakier-Gingras, Lea.
Landes Bioscience: Georgetown, Tex.
CODEN: 69FYBX; ISBN: 0-306-47839-0
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review. Aminoacyl-tRNA synthetases (aaRS) catalyze the esterification of a particular tRNA with its corresponding amino acid. In the first reaction step, the appropriate amino acid is recognized by the enzyme and reacts with ATP to form an enzyme-bound mixed anhydride; in the second step, this activated amino acid is esterified with one of the two hydroxyl groups of the tRNA. AaRSs are classified into two main groups of ten enzymes each, on the basis of common structural and functional features. The design of aaRS inhibitors has three main objectives: first, to facilitate the crystallization and X-ray structure determination of these enzymes; second, to gain mechanistic information about them; and third, to discover new antibiotics. Several natural products including pseudomonadic acid, SB-203207, SB-219383, indolmycin, capsaicin and ascamycin are selective inhibitors of aaRSs. Pseudomonadic acid is a potent inhibitor of bacterial IleRS and is the sole aaRS inhibitor currently marketed as an antibacterial agent. Synthetic inhibitors are usually stable analogs of the mixed anhydride intermediate. The stability is achieved by replacement of the labile anhydride function by nonhydrolyzable bioisosteres. Several aminoalkyl adenylates (replacement of the anhydride by a phosphate ester) and aminoacylsulfamoyl adenosines (replacement of the phosphate by a sulfamoyl group) have been synthesized and shown to be potent inhibitors of aaRSs.

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD
(6 CITINGS)
REFERENCE COUNT: 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2004:19695 HCAPLUS

Updated Search

stn

DOCUMENT NUMBER: 140:399078
TITLE: 4-Hydroxyphenylpyruvate dioxygenase as a drug discovery target
AUTHOR(S): Yang, Ding-Yah
CORPORATE SOURCE: Department of Chemistry, Tunghai University, Taichung, 407, Taiwan
SOURCE: Drug News & Perspectives (2003), 16(8), 493-496
CODEN: DNPEED; ISSN: 0214-0934
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The mol. mechanism for 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) inhibition by nitisinone, a recently approved new drug for the treatment of hereditary tyrosinemia type I, has been satisfactorily explained by its action as an analog to the substrate 4-hydroxyphenylpyruvate. In addition, a novel induced conformationally restricted 4-HPPD inhibitor, diketonitrile, which serves as a nonclassical bioisostere for rigid cyclic 1,3-diketone derivs., has been introduced. Further application of the mol. mode of action of nitisinone in rational design of potential inhibitors for α -ketoglutarate-coupled dioxygenases is discussed.

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:509718 HCAPLUS
DOCUMENT NUMBER: 139:373962
TITLE: Synthesis of new HIV protease inhibitors containing a novel (2-Phenylsulfanyl-1-hydroxyethyl)amide isostere
AUTHOR(S): Rocheblave, L.; Priem, G.; Courcambeck, J.; De Michelis, C.; Bonnet, B.; Chermann, J. C.; Kraus, J. L.
CORPORATE SOURCE: Laboratoire de Chimie Biomoléculaire, Faculté des Sciences de Luminy, Université de la Méditerranée, Marseille, 13288, Fr.
SOURCE: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 723-724.
Editor(s): Martinez, Jean; Fehrentz, Jean-Alain.
Editions EDK: Paris, Fr.
CODEN: 69EDWK; ISBN: 2-84254-048-4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review of the authors' work on designing new Amprenavir bioisosteres as anti-HIV agents.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:484474 HCAPLUS
DOCUMENT NUMBER: 140:22480
TITLE: Chemistry challenges in lead optimization: silicon isosteres in drug discovery

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AUTHOR(S): Showell, Graham A.; Mills, John S.
CORPORATE SOURCE: Cambridge Science Park, Amedis Pharmaceuticals Ltd.,
Cambridge, 162, UK
SOURCE: Drug Discovery Today (2003), 8(12), 551-556
CODEN: DDTQFS; ISSN: 1359-6446
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. During the lead optimization phase of drug discovery projects, the factors contributing to subsequent failure might include poor portfolio decision-making and a sub-optimal intellectual property (IP) position. The pharmaceutical industry has an ongoing need for new, safe medicines with a genuine biomedical benefit, a clean IP position and commercial viability. Inherent drug-like properties and chemical tractability are also essential for the smooth development of such agents. The introduction of bioisosteres, to improve the properties of a mol. and obtain new classes of compounds without prior art in the patent literature, is a key strategy used by medicinal chemists during the lead optimization process. Sila-substitution (C/Si exchange) of existing drugs is an approach to search for new drug-like candidates that have beneficial biol. properties and a clear IP position. Some of the fundamental differences between carbon and silicon can lead to marked alterations in the physicochem. and biol. properties of the silicon-containing analogs and the resulting benefits can be exploited in the drug design process. The challenges for the medicinal chemist in lead optimization are many fold. Key issues to be addressed include the identification of candidates with drug-like qualities and a novel intellectual property (IP) position. Both of these issues can be addressed with the use of novel bioisosteres. In this regard, silicon offers an exciting, but hitherto largely overlooked element, for use as a tetrahedral isostere of carbon in drug discovery and development. The use of silicon affords certain advantages over carbon, including that of a novel IP position.

OS.CITING REF COUNT: 41 THERE ARE 41 CAPLUS RECORDS THAT CITE THIS
RECORD (41 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:652167 HCAPLUS
DOCUMENT NUMBER: 138:198017
TITLE: Why do drugs look the way they do?
AUTHOR(S): Brill, Wolfgang K.-D.
CORPORATE SOURCE: Discovery Research Oncology, Pharmacia Corp.,
Nerviano, I-20014, Italy
SOURCE: Seminars in Organic Synthesis, Summer School "A.
Corbella", 27th, Gargnano, Italy, June 17-21, 2002 (2002), 157-191. Societa Chimica Italiana:
Rome, Italy.
CODEN: 69CZX9; ISBN: 88-86208-20-0
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review. The author addresses why certain features, such as being a heterocycle, are determining whether a mol. is drug-like. The interaction of a drug to its target must be sustained by specific interactions, which can only be provided between chemical functionalities of a drug and those of its target. If cyclic structures provide the highest clustering of atoms and,

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in organic mols., heteroatoms provide most functional groups, then the greatest d. of functionality can only be a heterocycle. Specific topics discussed include: biol. relevant targets, the "drug-likeness" of a small mol. dets. which target is drugable, which forces make drugs bind to their targets, how must a protein surface look like to allow tight binding with small hydrophobic mols., protein kinases as example for a drug target, how can drugs fill hydrophobic pockets, heterocycles as bioisosteres, and combinatorial synthesis of heterocycles.

REFERENCE COUNT: 217 THERE ARE 217 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:329208 HCAPLUS

DOCUMENT NUMBER: 137:241558

TITLE: The AMPA receptor binding site: focus on agonists and competitive antagonists
AUTHOR(S): Stensbol, Tine Bryan; Madsen, Ulf; Krosgaard-Larsen, Povl

CORPORATE SOURCE: NeuroScience PharmaBiotec Research Center, Department of Medicinal Chemistry, The Royal Danish School of Pharmacy, Copenhagen, DK-2100, Den.

SOURCE: Current Pharmaceutical Design (2002), 8(10), 857-872

CODEN: CPDEFP; ISSN: 1381-6128

PUBLISHER: Bentham Science Publishers

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. It is generally agreed that (S)-glutamic acid (Glu) receptors are involved in the development of a number of diseases in the central nervous system (CNS), and ligands that interact with these receptors are of significant interest. Selective ligands are indispensable as tools for the elucidation of the physiol. role of AMPA receptors and as leads for the development of therapeutic agents. Over the last decade a wide variety of such ligands have been developed and studies on the structure-activity relationships of these compds. have contributed to our understanding of the mechanisms involved in AMPA receptor activation and blockade. Series of selective agonists using the 3-isoxazolol amino acid ibotenic acid (2) as a lead compound have been designed and developed. Other heterocycles, such as the uracil moiety of willardiine (6), have also proved to be highly effective bioisosteres for the distal carboxyl group of Glu. For a number of reasons, the development of competitive antagonists with therapeutic potential has been hampered for example due to the limited solubility of key heterocyclic compds. structurally unrelated to Glu. However, some problems have been overcome, and series of water-soluble, potent and selective quinoxalinediones, indenoimidazones and isatine oximes have now been developed. At the turn of the millennium the crystal structure of GluR2 co-crystallized with different AMPA receptor ligands became available, opening a new era in the design of AMPA receptor ligands on a rational basis.

OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)

REFERENCE COUNT: 106 THERE ARE 106 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L6 ANSWER 7 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:248812 HCAPLUS

DOCUMENT NUMBER: 137:33457

TITLE: Glycodendrimers: novel glycotopes isosteres unmasking sugar coding. Case study with T-antigen markers from breast cancer MUC1 glycoprotein

AUTHOR(S): Roy, Rene; Baek, Myung-Gi

CORPORATE SOURCE: Centre for Research in Biopharmaceuticals, Department of Chemistry, University of Ottawa, Ottawa, ON, K1N 6N5, Can.

SOURCE: Reviews in Molecular Biotechnology (2002),

90(3-4), 291-309

CODEN: RMBIFZ; ISSN: 1389-0352

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with refs. Glycodendrimers are relatively novel synthetic biomacromols. that are made of biol. relevant carbohydrate ligands constructed at the periphery of a wide range of highly functionalized and repetitive scaffolds having varied mol. wts. and structures. They were aimed to fill the gap between glycopolymers, having generally dispersed higher mol. weight, and small glycoclusters, in the study of multivalent carbohydrate protein interactions. In a way, glycodendrimers, with their spheroidal or dendritic (wedge) type structures, were initially designed as bioisosteres of cell surface multiantennary glycans. They are now considered as potent inhibitors of microbial adhesins. They have also been shown to play some roles in signal transduction and in receptor crosslinking. This brief report will describe advances that have been made toward the syntheses of a range of glycodendrimers bearing the immunodominant T-antigen disaccharide [β -D-Gal-(1-3)- α -D-GalNAc] found on malignant cells of carcinomas, particularly related to breast cancer. This antigen, usually cryptic on healthy tissues, is greatly increased on cancer cells as a result of aberrant glycosylation. It is considered to be an important cancer marker. The synthesis of the T-antigen disaccharide will be briefly described, followed by the elaboration of neoglycoproteins and glycopolymers used to raise monoclonal antibodies against the T-antigen and for screening purpose, resp.

OS.CITING REF COUNT: 56 THERE ARE 56 CAPLUS RECORDS THAT CITE THIS RECORD (59 CITINGS)

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:132140 HCAPLUS

DOCUMENT NUMBER: 136:308556

TITLE: Highly efficient semisynthesis of biologically active epothilone derivatives

AUTHOR(S): Vite, Gregory D.; Borzilleri, Robert M.; Kim, Soong-Hoon; Regueiro-Ren, Alicia; Humphreys, W. Griffith; Lee, Francis Y. F.

CORPORATE SOURCE: Pharmaceutical Research Institute, Bristol-Myers Squibb Company, Princeton, NJ, 08543-4000, USA

SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents), 97-111

CODEN: ACSMC8; ISSN: 0097-6156

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PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Novel epothilone derivs. were prepared by both total synthesis and semisynthesis. Comparison of the two strategies suggests that a semisynthesis approach has several practical advantages including ease of preparation, stereochem. control, and potential for scale-up. Synthetic chemical

for efficient deoxygenation of epothilones, preparation of epoxide biososteres, and an efficient lactone-to-lactam conversion are presented. In vitro biol. data for the new epothilone analogs are provided, along with preliminary in vivo data for clin. candidate BMS-247550.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:872304 HCAPLUS

DOCUMENT NUMBER: 136:151211

TITLE: (α -Monofluoroalkyl)phosphonates: a class of isoacidic and "tunable" mimics of biological phosphates

AUTHOR(S): Berkowitz, David B.; Bose, Mohua
CORPORATE SOURCE: Department of Chemistry, University of Nebraska, Lincoln, NE, 68588-0304, USA

SOURCE: Journal of Fluorine Chemistry (2001), 112(1), 13-33

CODEN: JFLCAR; ISSN: 0022-1139

PUBLISHER: Elsevier Science S.A.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. In the early 1980s, Blackburn and McKenna suggested that α -fluorination might lead to phosphonates that better mimic natural phosphates. Although α -monofluorination produces phosphonates with "matching" second pKa values, the α,α -difluorinated phosphonates have received more attention in the past decade or so. Recently, reported enzyme kinetic data on the α -monofluorinated phosphonates from the O'Hagan laboratory and from our laboratory suggest that the CHF

stereochem. does affect enzyme-binding, thereby providing an addnl. variable that may be tuned to achieve optimal binding to an active site of interest. This asymmetry also appears in structural data from the groups of Barford/Burke and Tracey on PTP1B complexes with bound α,α -difluorinated phosphonate inhibitors. In those complexes, only one of two prochiral fluorine atoms appears to interact appreciably with the enzyme. Namely, it is thought that the pro-R (Fsi) fluorine is engaged in an important hydrogen bond with the Phe-182 amide NH. Available methods for the synthesis of this class of α -monofluorinated phosphonates are reviewed. A new convergent approach, developed at Nebraska, in which the potassium anion of (α -fluoro- α -phenylsulfonylethyl)methyl phosphonate is used to displace primary triflates is also described. This method is particularly convenient as it allows one to perform a "fluorinated phosphonate scan" of an active site of interest (in what follows, we use this expression to

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designate the synthesis and evaluation of a complete set of the CH₂-, CF₂- and both stereoisomeric CHF-phosphonates in an active site of interest) from a single primary triflate. The properties of the title compds. in enzyme active sites are discussed, as are possible interactions of these fluorine-containing bioisosteres with active site residues.

OS.CITING REF COUNT: 62 THERE ARE 62 CAPLUS RECORDS THAT CITE THIS RECORD (62 CITINGS)
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:578555 HCAPLUS
DOCUMENT NUMBER: 136:146443
TITLE: Studies on the synthesis of herbicides having five-membered heterocycles as the core skeleton
AUTHOR(S): Kudo, Noriaki
CORPORATE SOURCE: Agrosoci. Res. Lab., Sankyo Co., Ltd., 1041, Yasu, Yasu-cho, Yasu-gun, Shiga, 520-2342, Japan
SOURCE: Gifu Yakka Daigaku Kiyo (2001), 50, 49-60
CODEN: GYDKA9; ISSN: 0434-0094
PUBLISHER: Gifu Yakka Daigaku
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. Bioisoteric transformation of known bioactive compds. is one of the most efficient methods in drug design. If a new example of a bioisostere is found, it is possible to synthesize new bioactive compds., which have never been synthesized before, having a novel skeleton. The author set up the new bioisosteric hypothesis that a ring carbon-chlorine atom is bioisosteric to a carbon-alkylthio group and that a ring nitrogen atom is bioisosteric to a carbon-chlorine atom or a carbon-fluorine atom. To confirm this hypothesis, novel compds. were designed and synthesized, and their herbicidal activities were investigated.

L6 ANSWER 11 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:546779 HCAPLUS
DOCUMENT NUMBER: 135:313000
TITLE: The use of bioisosteric groups in lead optimization
AUTHOR(S): Olesen, Preben H.
CORPORATE SOURCE: Medicinal Chemistry Research, Novo Nordisk A/S, Maaloev, 2760, Den.
SOURCE: Current Opinion in Drug Discovery & Development (2001), 4(4), 471-478
CODEN: CODDF; ISSN: 1367-6733
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs. It is now half a century since Friedman introduced the term bioisosterism for the similar biol. activity of structurally related compds. Since then, the concept has been used extensively and successfully in the optimization of lead compds. in drug discovery. The number of chemical lead compds. has expanded enormously in recent years due to the expression of an increasing number of recombinant proteins, and the screening of these new protein targets against a large number of compds. in high-throughput screens. For the fine-tuning of lead compds. to obtain candidates suitable for clin. trials, which is in most circumstances still

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a tedious process, the use of bioisosteric replacement can be of significant value. This is especially the case in optimizing for selectivity for a specific target and in improving the pharmacokinetic properties of lead compds. The use of bioisosteres in lead optimization is illustrated by some recent examples from the literature.

OS.CITING REF COUNT: 34 THERE ARE 34 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:538924 HCAPLUS
DOCUMENT NUMBER: 135:352160
TITLE: SH2 domain inhibition: a problem solved?
AUTHOR(S): Shakespeare, W. C.
CORPORATE SOURCE: ARIAD Pharmaceuticals, Inc., Cambridge, MA, 02139-4234, USA
SOURCE: Current Opinion in Chemical Biology (2001), 5(4), 409-415
CODEN: COCBF4; ISSN: 1367-5931
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with refs. The past two years have witnessed a number of significant advances in the design of SH2 inhibitors of both Src and Grb2. For Src, several non-peptide templates have been developed with high affinity, and one case, in the context of bone-binding phosphotyrosine bioisostere, has yielded an in vivo active antiresorptive agent. Similarly, high-affinity Grb2 SH2 inhibitors with novel phosphotyrosine replacements have now been reported that demonstrate, for the first time, cellular activities consistent with an anticancer agent.

OS.CITING REF COUNT: 64 THERE ARE 64 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:456661 HCAPLUS
DOCUMENT NUMBER: 135:211174
TITLE: The Cyclohexene Ring as Bioisostere of a Furanose Ring: Synthesis and Antiviral Activity of Cyclohexenyl Nucleosides
AUTHOR(S): Herdewijn, P.; De Clercq, E.
CORPORATE SOURCE: Rega Institute for Medical Research, Laboratory of Medicinal Chemistry, K.U. Leuven, Minderbroedersstraat, Leuven, B-3000, Belg.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(12), 1591-1597
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 16 refs. on the application of the bioisosteric concept between a furanose ring and a cyclohexene ring in the nucleoside field has led to the discovery of new potent antiviral agents.

OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS

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REFERENCE COUNT: 16 RECORD (24 CITINGS)
THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:490729 HCAPLUS
DOCUMENT NUMBER: 133:249335
TITLE: The 2-pyridone antibacterial agents: Bacterial
topoisomerase inhibitors
AUTHOR(S): Li, Qun; Mitscher, Lester A.; Shen, Linus L.
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories,
Abbott Park, IL, 60064-6101, USA
SOURCE: Medicinal Research Reviews (2000), 20(4),
231-293
CODEN: MRREDD; ISSN: 0198-6325
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 132 refs. Many attempts have been made to prepare analogs of 4-quinolone antibacterial agents bearing novel ring systems, which might retain the favorable properties of these widely used antibacterial agents and at the same time increase activity against multidrug-resistant bacteria, streptococci, and anaerobic microorganisms. One such attempt involved bioisosteric exchange of the 1-N atom and 4a-C atom of naphthyridones, quinolones, and benzoxazines to produce a family of highly active pyridopyrimidines, quinolizines, and ofloxacin bioisosteres. These new antibacterial agents have been named collectively as the 2-pyridones. Many hundreds of 2-pyridones have been synthesized and evaluated in vitro and in vivo, and selected members are advancing toward human clin. trials. Preparation of these bioisosteres required the development of enabling chemical, as previous methods were unsuccessful in producing the needed core structures. This review compares the structure-activity relationships of these agents with known trends among 4-quinolones, from which it is seen that there are many parallels, but also some significant departures as well. Generally, 2-pyridones are more highly active in vitro and in vivo and more water soluble than comparable 4-quinolones. These properties are posited to arise from electronic and conformational alternations in these new substances. Selected members show excellent pharmacodynamic properties, justifying the view that this is a very promising new class of totally synthetic antibacterial agents.

OS.CITING REF COUNT: 65 THERE ARE 65 CAPLUS RECORDS THAT CITE THIS
RECORD (66 CITINGS)
REFERENCE COUNT: 133 THERE ARE 133 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L6 ANSWER 15 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1999:574966 HCAPLUS
DOCUMENT NUMBER: 131:294974
TITLE: The 2-pyridone antibacterial agents: 8-position
modifications
AUTHOR(S): Fung, Anthony K. L.; Shen, Linus L.
CORPORATE SOURCE: Infectious Disease Research, Pharmaceutical Discovery,
Abbott Laboratories, Abbott Park, IL, 60064-3500, USA
SOURCE: Current Pharmaceutical Design (1999), 5(7),
515-543

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CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 21 refs. Improved potency against multiply resistant streptococci and anaerobic microorganisms relative to current antibiotics has been sought by many labs. around the world. As one result of attempts to prepare analogs of 4-quinolone anti-infectives bearing novel ring systems, the 2-pyridones were discovered. The 2-pyridones, which are bioisosteres of 4-quinolones, are highly active against a wide range of resistant strains of bacteria. Several hundreds of 2-pyridones have been synthesized incorporating modifications at various positions. In order to reduce the complexity of this review, only the widely adopted 8-position modifications (corresponding to the 7-position of the quinolones) will be discussed here. From scientific publications and patents, it is clear that many of the 2-pyridones are very promising candidates and yet only selective members of these compds. have been advanced to detailed preclin. trials. Among the promising candidates, A-170568 was demonstrated to have the best overall profile in terms of the in vitro and in vivo antibacterial activities, safety profile, and tissue penetration.

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1999:23966 HCAPLUS
DOCUMENT NUMBER: 130:332046
TITLE: Heterocycles as bioisosteres for the α -carboxylate moiety of glutamate in AMPA receptor agonists: a review and theoretical study
AUTHOR(S): Greenwood, Jeremy R.; Vaccarella, Graziano; Capper, Hugh R.; Allan, Robin D.; Johnston, Graham A. R.
CORPORATE SOURCE: Adrien Albert Laboratory of Medicinal Chemistry, Department of Pharmacology, University of Sydney, 2006, Australia
SOURCE: Internet Journal of Chemistry [Electronic Publication] (1998), 1, No pp. Given, ARTICLE No. 38
CODEN: IJCHFJ
URL: <http://www.ijc.com/articles/1998v1/38/abstract.pdf>
PUBLISHER: Internet Journal of Chemistry
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review with 95 refs. (S)-2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) is the prototypical selective agonist for the AMPA subtype of excitatory amino acid (glutamate) receptors. Several 3-hydroxyisoxazole analogs are known to have activity at this receptor, as do a number of other alanine-substituted heterocyclic phenols, the acidic heterocycles being bioisosteres for the α -carboxylate moiety of glutamate. The increasingly diverse range of known AMPA agonists is reviewed, including a number of novel pyridazine-based analogs. By removal of a common glycine unit, the parent heterocycles 3-hydroxy-4,5-dimethylisoxazole, 3-hydroxy-4,5-dimethylisothiazole,

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4-methyl-5-isoxazolone, 3-hydroxy-4-methyl-1,2,5-thiadiazole, 2-methyl-3,5-dioxo-1,2,4-oxadiazolidine, 1-methyluracil, 6-aza-1-methyluracil, and 3-hydroxy-4-methylpyridazine 1-oxide are modeled as representative of the known α -carboxylate bioisosteres. In addition heterocyclic fragments of inactive hydantoin and 3,5-dioxotriazole quisqualate analogs, and pyridazinone fragments with derivs. of varying potency are considered. These structures and their conjugate bases are subjected to high level ab initio calcs. up to G2(MP2) theory, and semiempirical aqueous phase calcs. using the AM1-SM2 model. Their tautomerism and aqueous pKa behavior are studied in detail, and compared with exptl. data. Mol. geometries and electrostatic potential-derived charge distributions are presented. Electrostatic properties at the Van der Waals surface are compared. Calculated properties are discussed with respect to structural requirements for AMPA receptor activity. Tridentate models of AMPA receptor binding are presented.

L6 ANSWER 17 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1998:72629 HCAPLUS

DOCUMENT NUMBER: 128:212440

ORIGINAL REFERENCE NO.: 128:41893a,41896a

TITLE: A new class of diacidic nonpeptide angiotensin II receptor antagonists

AUTHOR(S): Naka, Takehiko

CORPORATE SOURCE: Pharmaceutical Research Laboratories 1, Takeda Chemical Industries, Ltd., Osaka, 532, Japan

SOURCE: Medicinal Chemistry: Today and Tomorrow, Proceedings of the AFMC International Medicinal Chemistry Symposium, Tokyo, Sept. 3-8, 1995 (1997), Meeting Date 1995, 89-96. Editor(s): Yamazaki, Mikio. Blackwell: Oxford, UK.

CODEN: 65ONAG

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review with 12 refs. Blockade of the action of angiotensin II (AII) has long been a target for development of novel antihypertensive agents. We recently discovered a novel class of potent nonpeptide AII receptor antagonists, benzimidazole-7-carboxylic acids (e.g., CV-11974). TCV-116, the prodrug of CV-11974, showed highly potent AII antagonistic and antihypertensive activities at oral administration. Structure-activity relationship (SAR) studies revealed that the adjacent arrangement of a lipophilic substituent, a tetrazolylbiphenyl moiety and a carboxyl group was the important structural requirement for potent AII antagonistic activity. Our efforts to find a new acidic bioisostere as a tetrazole replacement, resulted in the discovery of TAK-536 having 5-oxo-1,2,4-oxadiazole ring, which showed both potent AII antagonistic and antihypertensive activity and good oral bioavailability comparable to that of TCV-116.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1997:292735 HCAPLUS

DOCUMENT NUMBER: 127:8

ORIGINAL REFERENCE NO.: 127:2h,3a

TITLE: Developments in purine and pyrimidine receptor-based therapeutics

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AUTHOR(S): Spedding, Michael; Williams, Michael
CORPORATE SOURCE: Science Reunion, Servier, Nevilly sur Seine, Fr.
SOURCE: Drug Development Research (1997), Volume
Date 1996, 39(3/4), 436-441
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. Progress in the identification of novel P1 and P2 receptor ligands has continued to lag behind the explosion in receptor cloning, especially in the P2 area. Nonetheless, a number of novel chemical entities and natural receptor ligands are continuing to advance in clin. trials or, alternatively have become important new tools to study receptor function. Compds. of note with activity at the P1 receptor family include NNC 21-0136 (A1 agonist; preclin.; stroke); SCH 59761 (nonselective P1 agonist; preclin.; cardiovascular disorders); the A1 antagonists, KFM-19 (BIIP-20; phase II) and MDL 102,503 development (status unknown) that may have therapeutic potential as cognition enhancers. KF 17837 and related A2A-antagonists such as KW 6002 represent potential novel treatments for Parkinson's disease. SCH 58261 (A2A receptor antagonist; preclin.) is a novel nonxanthine antagonist ligand. KW 3902 (phase II), FK-453/FK 113453 (possibly discontinued) and CVT-124 (phase I) are A1 receptor-selective xanthine-based antagonists that have potential in the treatment of renal diseases. NNC 53-0055 (preclin.) is the first of a new series of selective A3 receptor agonists that modulate cytokine production MRS 1067, MRS 1067, MRS 1097, MRS 1222, L-249, 313, and L-268, 605 (all preclin.) represent new A3-receptor antagonists. GP 3269 (preclin.) is an adenosine kinase inhibitor with potential efficacy in septic shock, stroke, and pain. ARL 67085 (phase II) is an ATP bioisostere that is an antagonist of the P2T receptor that is the first of new generation of antithrombotic agents. Systemic ATP has reached phase II trials as a novel approach to metastasis regression. The pyrimidine nucleotide, UTP (phase II) is being examined as P2Y2 receptor agonist for the treatment of cystic fibrosis.
OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L6 ANSWER 19 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1996:710166 HCAPLUS
DOCUMENT NUMBER: 126:6
ORIGINAL REFERENCE NO.: 126:3a
TITLE: Bioisosterism: A rational approach in drug design
AUTHOR(S): Patani, George A.; LaVoie, Edmond J.
CORPORATE SOURCE: College of Pharmacy, Rutgers The State University of New Jersey, Piscataway, NJ, 08855-0789, USA
SOURCE: Chemical Reviews (Washington, D. C.) (1996), 96(8), 3147-3176
CODEN: CHREAY; ISSN: 0009-2665
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 191 refs., on bioisosteres that incorporates sufficient detail to enable the reader to understand the concepts being

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delineated. Classical bioisosteres, such as monovalent atoms and groups, divalent isosteres, trivalent atoms and groups, tetra substituted atoms, and ring equivalent, and non-classical bioisosteres, such as cyclic vs. non-cyclic non-classical bioisosteric replacements and non-classical bioisosteric replacements of functional groups, are discussed.

OS.CITING REF COUNT: 331 THERE ARE 331 CAPLUS RECORDS THAT CITE THIS RECORD (331 CITINGS)
REFERENCE COUNT: 191 THERE ARE 191 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1996:74550 HCAPLUS
DOCUMENT NUMBER: 124:137953
ORIGINAL REFERENCE NO.: 124:25467a,25470a
TITLE: Synthetic pro-oxidants: Drugs, pesticides and other environmental pollutants
AUTHOR(S): Stohs, Sidney J.
CORPORATE SOURCE: School Pharmacy and Allied Health Professions, Creighton University, Omaha, NE, 68178, USA
SOURCE: Oxidative Stress and Antioxidant Defenses in Biology (1995), 117-80. Editor(s): Ahmad, Sami. Chapman & Hall: New York, N. Y.
CODEN: 62FOAL
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with many refs. in which the abilities of various chemical related groups of compds. to induce the formation of reactive oxygen species, and produce an oxidative stress with resultant tissue damaged are discussed. Haloalkanes, polyhalogenated cyclic pesticides, phorbol esters, paraquat and diquat, quinones, quinolones, dioxin and its bioisosteres, transition metals, and cation complexes are reviewed.

OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

L6 ANSWER 21 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1996:24099 HCAPLUS
DOCUMENT NUMBER: 124:75379
ORIGINAL REFERENCE NO.: 124:13753a,13756a
TITLE: Anthracene-9,10-diones and aza bioisosteres as antitumor agents
AUTHOR(S): Krapcho, A. Paul; Maresch, Martin J.; Hacker, Miles P.; Hazelhurst, Lori; Menta, Ernesto; Oliva, Ambrogio; Spinelli, Silvano; Beggiolin, Gino; Giuliani, Fernando C.; et al.
CORPORATE SOURCE: Dep. Chem. Pharmacol., Univ. Vermont, Burlington, VT, 05405, USA
SOURCE: Current Medicinal Chemistry (1995), 2(4), 803-24
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers BV
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 158 refs. Naturally occurring quinones which structurally consist of an anthracene-9,10-dione chromophore are important antitumor

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agents. The anthracycline antibiotics, in particular, doxorubicin, are major chemotherapeutic agents. The pluramycins and the ene-dienes antibiotics also show promise as antitumor drugs. The synthetic anthracene-9,10-diones such as mitoxantrone are potent antitumor agents. Analogs related to mitoxantrone have been synthesized and biol. evaluated. Aza and diaza bioisosteres related to the anthracene-9,10-diones have been prepared and evaluated and several of these chemotypes show promise for development as anticancer agents. This review will discuss the discovery of cytotoxic anthracene-9,10-diones and the synthesis and antitumor properties of the related aza and diaza bioisosteres.

OS.CITING REF COUNT: 54 THERE ARE 54 CAPLUS RECORDS THAT CITE THIS RECORD (54 CITINGS)

L6 ANSWER 22 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1995:970984 HCAPLUS

DOCUMENT NUMBER: 124:44541

ORIGINAL REFERENCE NO.: 124:8135a,8138a

TITLE: P2-purinoreceptors: Advances and therapeutic opportunities

AUTHOR(S): Williams, Michael; Jacobson, Kenneth A.

CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA

SOURCE: Expert Opinion on Investigational Drugs (1995), 4(10), 925-34

CODEN: EOIDER; ISSN: 0967-8298

PUBLISHER: Ashley Publications

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 52 refs. The recent cloning of a number of distinct receptors belonging to the P2-purinoreceptor superfamily has provided conclusive evidence for a pivotal role for ATP and other nucleotides as effector mols. involved in cell-to-cell communication and the modulation of many basic aspects of tissue function. ATP itself is being clin. evaluated as a cytotoxic agent for the treatment of cancer and as an adjunct to inhalation anesthetic use. The pyrimidine nucleotide, UTP, is in clin. trials for the treatment of cystic fibrosis. The stable ATP bioisostere, ARL 67085, is being developed as a novel antithrombotic agent, blocking with a superior safety profile and increased efficacy as compared to other agents. The diversity of P2 receptors, with eleven having been defined using both pharmacol. and mol. cloning criteria, indicates considerable addnl. potential and subtlety in regard to the effects of ATP on tissue function and pathophysiol.

OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

L6 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1995:886601 HCAPLUS

DOCUMENT NUMBER: 123:305844

ORIGINAL REFERENCE NO.: 123:54499a,54502a

TITLE: Bioisosteric replacement and development of lead compounds in drug designs

AUTHOR(S): Zhao, Guofeng; Yang, Huazeng

CORPORATE SOURCE: Inst. Elemental Org. Chem., Nankai Univ., Tianjin, Peop. Rep. China

SOURCE: Huaxue Tongbao (1995), (6), 34-8

CODEN: HHTPAU; ISSN: 0441-3776

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PUBLISHER: Kexue
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review with 10 refs. discussing roles of bioisosteric replacement and development of lead compds. in drug designs. Design of antihistaminic imidazole compds. is given as an example.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L6 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1995:673233 HCAPLUS
DOCUMENT NUMBER: 123:75017
ORIGINAL REFERENCE NO.: 123:13094h,13095a
TITLE: Structure-activity relationships of melatonin analogs
AUTHOR(S): Caignard, Daniel-Henri; Lesieur, Daniel; Depreux, Patrick; Renard, Pierre; Delagrance, Philippe; Guardiola-Lemaitre, Beatrice
CORPORATE SOURCE: ADI/Institut de Recherches Internationales Servier, Courbevoie, 92415, Fr.
SOURCE: European Journal of Medicinal Chemistry (1995), 30(Suppl., Proceedings of the 13th International Symposium on Medicinal Chemistry, 1994), 637s-42s
CODEN: EJMCAS; ISSN: 0223-5234
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 14 refs. It has been demonstrated that the indole ring of melatonin is not an essential characteristic of the mol. for either its affinity for the melatonin receptor or for its biol. activity, as it can be replaced by a naphthalene bioisostere. While substitution of the nitrogen in the indole ring by either S (benzothiophene) and O (benzofuran) can be tolerated, they both reduce binding affinities to some extent, and the latter substitution elicits effects which cannot be presently explained. Homologous extension of the N-acetyl side chain of the naphthalenic analog together with other modifications can increase the affinity of the compds. for the melatonin receptor over that of melatonin itself. Furthermore some of these modifications have produced analogs which show biphasic rather than monophasic binding curves. Such data would be consistent with either the presence of two distinct receptor subtypes or detection of the receptor in two different affinity states.

L6 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1994:6 HCAPLUS
DOCUMENT NUMBER: 120:6
ORIGINAL REFERENCE NO.: 120:1a
TITLE: Application of bioisosterism to new drug design
AUTHOR(S): Yun, Sung Hwa
CORPORATE SOURCE: Ind. Chem. Dep., Azu Univ., S. Korea
SOURCE: Hwahak Sekye (1993), 33(8), 576-9
CODEN: HWSEEX; ISSN: 1225-004X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Korean

AB A review with 5 refs. which discusses definition of isosteres, application of bioisosterism for mol. modification, and some recent examples of nonclassical isosteres for drug improvement in potency, selectivity, and duration of action.

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L6 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1993:616556 HCAPLUS
DOCUMENT NUMBER: 119:216556
ORIGINAL REFERENCE NO.: 119:38313a,38316a
TITLE: Studies of a novel series of thiazole-containing
5-hydroxytryptamine-3 receptor antagonists
AUTHOR(S): Rosen, Terry; Nagel, Arthur A.; Rizzi, James P.
CORPORATE SOURCE: Centr. Res. Div., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Drug Des. Neurosci. (1993), 213-30, 4
plates. Editor(s): Kozikowski, Alan P. Raven: New
York, N. Y.
CODEN: 59IIAM
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with 30 refs. on a novel series of 5-HT3 receptor antagonists.
Computer modeling studies were utilized to identify a hypothetical
pharmacophore for 5-HT3 receptor binding. This model was utilized to
rationalize observed SAR as well as to guide SAR development. The modeling
studies and SAR results suggest that the thiazole moiety in this series of
agents is acting as a carbonyl bioisostere. Several of the
comps. were shown to exhibit potent 5-HT3 receptor antagonism in vivo as
well as penetrate the blood-brain barrier upon peripheral administration.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)

L6 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1992:59240 HCAPLUS
DOCUMENT NUMBER: 116:59240
ORIGINAL REFERENCE NO.: 116:10249a,10252a
TITLE: Synthesis and pharmacological evaluation of
4,4a-dihydro-5H-[1]-benzopyrano[4,3-c]pyridazin-3(2H)-
ones: bioisosteres of antihypertensive and
antithrombotic benzo[h]cinnolinones
AUTHOR(S): Winwood, David
CORPORATE SOURCE: Xenon Vision, USA
SOURCE: Chemtracts: Organic Chemistry (1991), 4(4),
312-15
CODEN: CMOCEI; ISSN: 0895-4445
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB The title research of G. Cignarella, et. al (1990) is reviewed with
commentary and 4 refs.

L6 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1991:647268 HCAPLUS
DOCUMENT NUMBER: 115:247268
ORIGINAL REFERENCE NO.: 115:41837a,41840a
TITLE: The substituent parameter database: a powerful tool
for QSAR analysis
AUTHOR(S): Boyd, Donald B.; Seward, Catherine M.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,
46285, USA
SOURCE: Pharmacochemistry Library (1991), 16(QSAR:
Ration. Approaches Des. Bioact. Compd.), 167-70
CODEN: PHLDIQ; ISSN: 0165-7208

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DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 19 refs. The substituent parameter database has proved to be a powerful tool for computer-assisted mol. design studies. QSAR, which has been particularly successfully in mol. design, is greatly expedited by having the database available for retrieving data, identifying potential bioisosteres, and devising SAR strategies to maximum the amount of information derivable from each compound synthesized.

L6 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1991:441128 HCAPLUS

DOCUMENT NUMBER: 115:41128

ORIGINAL REFERENCE NO.: 115:6941a,6944a

TITLE: Antagonistic amino acids and carbohydrates from microbial sources

AUTHOR(S): Inouye, Shigeharu; Sezaki, Masaji

CORPORATE SOURCE: Pharm. Res. Cent., Meiji Seika Kaisha, Ltd., Yokohama, 222, Japan

SOURCE: Meiji Seika Kenkyu Nenpo (1990), (29), 43-122

CODEN: MSKNA9; ISSN: 0465-6105

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

AB A review, with 315 refs., on antimetabolic amino acid analogs AL-719, MK1812, SF2369, SF1836, SF2185, SF2312, SF2448, SF1346, SF2538, SF1293, SF1293B, SF2253, HS-1, SF2339, and SF2513. Carbohydrate analogs include nojirimycin, its derivs., SF-666A, oligostatins, and SF1768. Their screening methods and structure-activity relationships are discussed. Topics also include bioisosteres of natural amino acids and carbohydrates.

L6 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1990:490746 HCAPLUS

DOCUMENT NUMBER: 113:90746

ORIGINAL REFERENCE NO.: 113:15079a,15082a

TITLE: Acidic isostere design: synthetic strategies and recent progress in understanding electronic properties and metabolic stability

AUTHOR(S): Lipinski, Christopher A.; Chenard, Bert L.

CORPORATE SOURCE: Pfizer Cent. Res., Groton, CT, 06340, USA

SOURCE: Pesticide Science (1990), 29(2), 227-40

CODEN: PSSCBG; ISSN: 0031-613X

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 34 refs. The efficient synthesis of a family of twelve acidic heterocycles (mercaptoazoles) of varying acidity from a single common intermediate facilitates the search for new acidic bioisosteres. An extension of this chemical approach led to a new family of phosphonate replacements in prototypes related to the N-methyl-D-aspartate (NMDA) antagonist 2-amino-7-phosphonheptanoic acid (AP7). Acidic isostere design may be facilitated by grouping hydroxylic heterocyclic carboxylic isosteres into one of two electronic classes based on the Gandour hypothesis. The limitations of normal hydroxamic acids as carboxylic acid surrogates suggest that the excellent metabolic stability of reverse hydroxamic acids may be useful in prospective acidic isostere design.

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OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD
(5 CITINGS)

L6 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1987:12094 HCAPLUS
DOCUMENT NUMBER: 106:12094
ORIGINAL REFERENCE NO.: 106:1977a,1980a
TITLE: Bioisosterism in drug design
AUTHOR(S): Lipinski, Christopher A.
CORPORATE SOURCE: Pfizer Cent. Res., Groton, CT, 06340, USA
SOURCE: Annual Reports in Medicinal Chemistry (1986
, 21, 283-91
CODEN: ARMCBI; ISSN: 0065-7743

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 94 refs. on bioisosteres (groups of mols. which
have chemical and phys. similarities producing broadly similar biol.
properties) in drug design. Bioisosterism is part of the spectrum of
QSAR.

OS.CITING REF COUNT: 37 THERE ARE 37 CAPLUS RECORDS THAT CITE THIS
RECORD (37 CITINGS)

L6 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1981:532571 HCAPLUS
DOCUMENT NUMBER: 95:132571
ORIGINAL REFERENCE NO.: 95:22195a,22198a
TITLE: Bioisosteric thiophenes
AUTHOR(S): Boehm, Ralf
CORPORATE SOURCE: Sekt. Pharm., Martin-Luther-Univ., Halle-Wittenberg,
Ger. Dem. Rep.
SOURCE: Wissenschaftliche Zeitschrift -
Martin-Luther-Universitaet Halle-Wittenberg,
Mathematisch-Naturwissenschaftliche Reihe (1981), 30(2), 3-16
CODEN: WMHMAP; ISSN: 0043-6887

DOCUMENT TYPE: Journal; General Review
LANGUAGE: German

AB A review with 59 refs.

L6 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1974:499125 HCAPLUS
DOCUMENT NUMBER: 81:99125
ORIGINAL REFERENCE NO.: 81:15637a,15640a
TITLE: Bioisosteres of the indole messengers
AUTHOR(S): Campaigne, E.; Maickel, R. P.; Bosin, T. R.
CORPORATE SOURCE: Dep. Chem., Indiana Univ., Bloomington, IN, USA
SOURCE: Med. Chem., Spec. Contrib. Int. Symp., 3rd (1973), Meeting Date 1972, 65-81. Editor(s):
Pratesi, P. Butterworth: London, Engl.
CODEN: 28VOAV

DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with 31 refs. of the preparation and structure-activity relations of
indole messenger bioisosteres.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)

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L6 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1967:1259 HCAPLUS

DOCUMENT NUMBER: 66:1259

ORIGINAL REFERENCE NO.: 66:239a,242a

TITLE: Certain aspects of methods and hypotheses of research
in chemical therapeutics

AUTHOR(S): Lespagnol, Albert; Lespagnol, Charles

CORPORATE SOURCE: Fac. Med. Pharm., Lille, Fr.

SOURCE: Chim. Ther. (1966), 66(3), 190-201; (4),
249-60; (5-6), 359-72

CODEN: CHTQAC

DOCUMENT TYPE: Journal

LANGUAGE: French

AB A review with 73 references. Covered are the concepts of
bioisosteres (those having the same type of biol. activity),
structural antagonists, homologous series, and certain practical
applications.

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